3007-9

THE AMERICAN REVIEW OF TUBERCULOSIS

JOURNAL OF
THE NATIONAL TUBERCULOSIS ASSOCIATION

EDITOR
ALLEN K. KRAUSE, Tucson, Arizona

EDITORIAL STAFF

E. R. BALDWIN, Saranac Lake, N. Y.
LAWRASON BROWN, Saranac Lake, N. Y.
H. J. CORPER, Denver, Col.
H. R. M. LANDIS, Philadelphia, Pa.
ESMOND R. LONG, Philadelphia, Pa.
J. A. MYERS, Minneapolis, Minn.
HENRY SEWALL, Denver, Col.

VOLUME XXVII
JANUARY-JUNE, 1933

9726
A1 V.27, 1933
6/25/34

PUBLISHED MONTHLY
AT MT. ROYAL AND GUILFORD AVENUES, BALTIMORE, MD.
BY THE NATIONAL TUBERCULOSIS ASSOCIATION

CONTENTS: ORIGINAL ARTICLES

NUMBER 1, JANUARY, 1933

The Fixity of the Attenuation of BCG. A. CALMETTE..... 1
Protection against Tuberculosis with BCG in Guinea Pigs. KONRAD E. BIRKHAUG..... 6
Tuberculosis and Leukaemia. R. H. JAFFÉ..... 32
Benign Pulmonary Tuberculosis with Diabetes. H. WESSLER AND HERMAN HENNELL..... 47
Congenital Cystic Disease of the Lung. WILLIAM C. POLLOCK AND HORACE P. MARVIN..... 59
Spontaneous Pneumothorax with Acute Abdominal Symptoms. WALDO R. OECHSLI AND JANE SKILLEN..... 67
Fluoroscopy in Tuberculosis Case-Finding. H. W. HETHERINGTON AND E. W. FLAHIFF..... 71
The Tuberculosis Trained Nurse. JOSEPH WALSH..... 81
The Costa and Red-Cell Sedimentation Reactions in Laryngeal Tuberculosis. CHARLES L. RUBENSTEIN..... 92
A Protest against the Current Conception of Activity in Pulmonary Tuberculosis. LOUIS H. FALES..... 101

NUMBER 2, FEBRUARY, 1933

Recent Developments in our Knowledge of Tuberculosis. J. ARTHUR MYERS..... 121
Pulmonary Roentgenography of Small Experimental Animals. SIDNEY GREENBERG..... 137
Localized Experimental Tuberculosis of the Lungs. ROBERT G. BLOCH..... 143
A Comparison of the Pathological Changes in Embolic Tuberculous and Pyogenic Pulmonary Abscesses. PHILIP H. PIERSON..... 150
Tuberculoma of the Brain. ERNEST SCOTT AND GRANT O. GRAVES.. 171
So Called Pleuropulmonary Endothelioma. ANDREW L. BANYAI AND JOHN GRILL..... 193
The Effects of Thoracoplasty on the Heart. OLGA S. HANSEN AND HENRY W. MALY..... 200
The Dietary Treatment of Skin Tuberculosis. S. BOMMER..... 209

NUMBER 3, MARCH, 1933

Alcohol and Tuberculosis. LAWRASON BROWN AND JOSEPH T. EAGAN..... 217
Change of Climate and Altitude. I. Its Effects on Tuberculosis Patients. E. W. PHILLIPS..... 247
A Comparison of Certain Media for the Cultivation of Tubercle-Bacilli from Sputum. M. F. SHAFFER..... 259
A Comparison of Tissue Reactions to Pulmonary Infection with Tubercle Bacilli in Animals of Varying Resistance. ARTHUR J. VORWALD..... 270
The Sensitization of Guinea Pigs and the Production of Allergy and Anaphylaxis to Tuberculoprotein. H. S. REICHLE AND HARRY GOLDBLATT..... 291
A Tape Test with Tuberculin Ointment. ERNST WOLFF..... 308
A Method of Recording Roentgen-Ray Readings. H. B. PIRKLE..... 311

NUMBER 4, APRIL, 1933

The Rôle of Emotion in Tuberculosis. MARY B. EYRE..... 315
The Gastric Function in Pulmonary Tuberculosis. SEYMOUR J. COHEN..... 330
The Blood-Pressure in Tuberculosis. A. R. MASTEN..... 342
Generalized Tuberculosis Complicated by Presence of Yeast-Like Organisms. HENRY W. FERRIS..... 348
The Closure of Adherent Tuberculous Cavities by Combined Artificial Pneumothorax and Phrenicectomy. PAUL SLAVIN..... 355
The Effects of Codliver-Oil Concentrate Injections. BURGESS GORDON AND R. J. TITHERINGTON..... 368
An Appliance for Immobilization in Pulmonary Tuberculosis. S. C. DAVIS..... 375
Tuberculin and the Schilling Blood Differential Count in the Diagnosis and Classification of Tuberculosis. J. F. BREDECK..... 377
The Effect of Tuberculin on Spermatozoa from Normal and Tuberculous Guinea Pigs. LILIAN C. DONALDSON AND ARTHUR J. VORWALD..... 401

NUMBER 5, MAY, 1933

The Pathological Anatomy of Pulmonary Tuberculosis in the American Negro and in the White Race. FRANKLIN R. EVERETT..... 411
The Comparative Sensitiveness of the Pirquet and the Intracutaneous Tuberculin Tests. JOSEPH D. ARONSON, DAVID ZACKS AND J. J. POUTAS..... 465

Tuberculosis and Tuberculous Infection among Nurses. SIDNEY J. SHIPMAN AND ELIZABETH A. DAVIS..... 474
The Correlation of Blood Counts in 150 Clinical Cases of Tuberculosis and Underlying Pathological Changes as Shown by Serial X-Ray Films. JOHN W. FLINN, ROBERT S. FLINN AND ZEBUD M. FLINN..... 488
The Use of Filtered-Air Chambers in Pulmonary Tuberculosis. ALVAN L. BARACH..... 508
The Sanatorium Treatment of Lupus. LOUIS ALPERT..... 515
Some Aspects of Artificial-Pneumothorax Technique. J. W. CUTLER. 522

NUMBER 6, JUNE, 1933

Preventive and Therapeutic Measures in Tuberculosis since Koch. EDGAR MAYER..... 529
Spontaneous Pneumothorax with Aortic Aneurysm and Pulmonary Fibrosis. CLARENCE H. KETTERER..... 553
Studies on the Pathogenesis of Primary Tuberculous Infection. I. The Regressive Lesions. HENRY C. SWEANY..... 559
Studies on the Pathogenesis of Primary Tuberculous Infection. II. Tendencies in Adult Primary Tuberculous Infection. HENRY C. SWEANY..... 575
A Study of Tuberculous Infection by way of the Female Genital Tract. EDWIN M. JAMESON..... 589
The Production of Tuberculous Tissue and Hypersensitiveness to Tuberculin in Guinea Pigs. C. H. BOISSEVAIN..... 595
A Study of So-Called Skin Lesions of Tuberculin-Reacting Cattle. LYMAN L. DAINES AND HAROLD AUSTIN..... 600
Tuberculosis Dispensary Practice in New Haven, Connecticut. H. R. EDWARDS..... 611

THE FIXITY OF THE ATTENUATION OF BCG

A. CALMETTE

More than a million children have now been vaccinated with *BCG* the world over, 425,000 of them in France (March 1, 1932), 204,000 in Indo-China, 100,000 in Rumania, 20,000 in Spain, 14,000 in Uruguay, etc. A large number of clinicians, accoucheurs and specialists in infants' diseases have devoted themselves since 1924 to the study of the immediate and late effects of this vaccination in nearly every civilized country, and it may seem superfluous to discuss the question, if *BCG* is to be considered as a fixed virus, the events having furnished sufficient answer to the question.

Nevertheless, it seems necessary to take the subject once more into consideration, because of the attacks of the adversaries of the method, who continue to publish their doubts on the matter. It is doubt on the fixity of *BCG* that still restrains those who fear to engage their responsibility and who refuse to advocate *BCG* vaccination. Consequently it may not be superfluous to estimate the value of the theoretical and experimental arguments against *BCG*, as published by different authors.

These arguments derive from experiments by which certain authors believe to have restored the virulence of *BCG* for guinea pigs and rabbits by some laboratory artifice. But nobody ever succeeded in rendering *BCG* virulent for bovines, sheep, swine or apes; and not a single clinician or pathologist in the world has been able to prove that one could isolate virulent *BCG* from the organs of a child vaccinated with *BCG*, and who died some time afterward.

We actually possess more than 400 protocols of autopsies of children, who died under the above-mentioned conditions.[1] Many *BCG* cultures

[1] We cite in the first place the important research work by J. Zeyland and Mrs. Piazecka-Zeyland, who studied the organs of 88 vaccinated children who died of different nontuberculous diseases; the authors succeeded in isolating 16 different pure *BCG* strains from mesenteric lymph nodes. We also cite Leon Bernard and Robert Debré (Paris); J. Parisot and Saleur (Nancy); Devun (St. Etienne); Leuret (Bordeaux); Rohmer and Chaussinand (Strasbourg); and, in other countries, C. Prausnitz, I. Zadek, H. Buschmann in Germany; J. Cantacuzene, Ciuca, Nasta, Veber and Alexa in Rumania; L. Saye in Spain; Malvoz and J. van Beneden in Belgium; Tzeknowitzer, Iakhnis and the Ukrainian Commission at Kharkoff; Moreau in Montevideo; William H. Park and his coworkers in New York, etc.

have been obtained from the lymph nodes in children, who died from two to nearly five months (P. Zeyland, 140 days) after having been vaccinated with *BCG*. These cultures had exactly the same attenuated character as the original *BCG* cultures. They were incapable to cause progressive lesions.

A certain number of babies have been inadvertently vaccinated by a subcutaneous injection of enormous doses of *BCG*, destined to absorption *per os*. One of these children got a cold abscess that had to be emptied by puncture, but it remained localized at the point of injection. The others had no symptoms at all. I know one of these children personally; it was born of a tuberculous mother, and is now 7 years old, and in perfect condition. I know equally well of a similar case in a neighboring country, caused by an ill-interpreted telephone call: 23 children of 4 to 14 years got subcutaneous injections of 10 instead of 0.02 mgm. They all developed a cold abscess, that regressed spontaneously in 13 cases, the others necessitating puncture. But they all remained in good health, and the "incident," which took place several years ago, had no evil consequences.

One could not wish a better proof of the perfect harmlessness and fixity of *BCG*.

Even premature or deformed babies may be treated with *BCG* without the least detriment. This is shown by a curious observation by R. Chaussinand and Tempe.[2] A hydrocephalic monster in Röhmer's Hospital, Strasbourg, got an intraperitoneal injection of 2 mgm. *BCG*, suspended in 80 cc. of saline solution to assure a better dispersion of the bacilli in the organism. The infant has supported the injection perfectly; it showed no fever and no loss of weight. A fortnight after the injection it had a positive tuberculin reaction. It was then sent to the children's hospital in Basel, where it died four months later of hydrocephalus and a too energetic vigantol treatment. No tuberculous lesions could be found at autopsy, and the guinea pigs inoculated with its mesenteric lymph nodes remained normal.

Consequently no clinical or pathological facts can be alleged to justify a doubt on the perfect stability of *BCG* in the human organism. And if some people insist on waiting 20 years to be sure that *BCG* really does not change, their fears seem somewhat exaggerated; the more so since 10 years of clinical observation taught us that tuberculin allergy and resistance against virulent superinfections vanish after some years in vaccinated individuals by a slow destruction and elimination of the *BCG*

[2] *Annales de l'Institut Pasteur*, July, 1930, xlv, 65.

bacilli. This process of elimination takes about 5 or 6 years in children, and 18 months or 2 years in bovines. That is why it is necessary to maintain immunity in vaccinated individuals by periodical revaccinations, until they are full-grown.

What can be the value of the exceptional observations, reported by S. A. Petroff and his coworkers, by E. S. Watson, Hormaeche, Satero del Rio, Sasano and Medlar, Dreyer and Vollum, Seiffert, Tiedemann, or the incompletely observed facts reported by Chiari, Nobel and Sole, Galli-Valerio, Korschun, Dwijkow and Gorochownikowa, Hutyra and Schutz? What do such disparate findings mean in face of hundreds of thousands of children, vaccinated the world over since 1924, and of whom not a single one ever presented any pathological symptoms that could be attributed to *BCG*? All these authors experimented on guinea pigs and rabbits, and the conditions in which they worked do not give sufficient guarantee against experimental errors. Their experiments are supposed to prove the possibility of an eventual return to virulence of *BCG*, but they constantly omitted to protect their animals efficiently against accidental or spontaneous contaminations.

The publications of Stanley Griffith and Douglas, Sewall and Max Lurie, Opie, Perla, O. Feierabend, Bruno Lange, W. Kolle, Coulaud, Truche, A. Saenz,[3] etc., have taught us that spontaneous tuberculosis is much less exceptional in guinea pigs and rabbits than we thought for a long time. Spontaneous tuberculosis is even relatively frequent in animals that are kept a very long time in the laboratory animal-room, especially when they are fed with bread or grass, that may have been contaminated by tuberculous sputum, as is often the case in laboratories belonging to a hospital or a sanatorium.

So we have a right to attribute the very exceptional cases of virulent tuberculosis in animals inoculated with *BCG*, observed by certain authors, to such fortuitous contaminations.

There is another error to which experimenters are exposed: they may be tempted to take cases of pseudotuberculosis in guinea pigs for true tuberculosis. There may be such a striking likeness between the two, that it is necessary to make stained smears of the organs and cultures to ascertain the right diagnosis.

Is it not possible that the facts, reported by E. A. Watson, S. A. Petroff, and some other authors, are due to such errors? The first reports having inoculated large doses of *BCG* culture (20 to 100 mgm.) in hundreds of

[3] *Soc. de Biologie*, February 13, 1932, cix, 437.

guinea pigs, which he kept at least 18 months, and to have found in 1 to 2 per cent of these animals authentic, progressive, transmissible tuberculous lesions; all the other guinea pigs, inoculated with the same huge doses, remained normal.

On the other hand Uhlenhuth and Seiffert, àpropos of the Lübeck episode, supported the rather paradoxical thesis that one positive experiment (and they consider Seiffert's experiment as such) has a greater value than a multitude of negative results from the most important laboratories of the world. This most extraordinary opinion has been most vigorously refuted by W. Kolle.

Moreover, thousands and thousands of guinea pigs and rabbits have now been inoculated with every imaginable dose of *BCG* by the most qualified experimenters. A certain number of such animals have been kept alive by us for a period of over $2\frac{1}{2}$ years,—much longer than in E. A. Watson's and S. A. Petroff's work. Animal passages have been made in great numbers by us and by everyone else. We never saw progressive and transmissible tuberculous lesions develop in such animals. And when Petroff claims to have dissociated *BCG* by Arkwright's and de Kruif's method, and to have obtained avirulent R-type colonies and very few virulent S-type colonies (1 S colony for about 35,000 Rs), he must realize by now that he may have been the victim of a technical error. This has been proved by ourselves, and since then by Neufeld and Bruno Lange in the Robert Koch Institute, Berlin, as well as by F. Gerlach in Vienna, C. Prausnitz in Breslau, Tzeknowitzer in Kharkoff, William H. Park in New York, Cantacuzene and his coworkers in Bucarest, Watanabe in Tokio, etc.

Hormaeche (Montevideo) has published an experiment, which he has never been able to reproduce and by which he states to have shown that *BCG* may become virulent when it is associated with other bacteria, for instance, *Streptococcus caviae.* Dreyer and Vollum think that deep cultures of *BCG* in veal-broth may become virulent, and Much believes that the same may be said of *BCG* cultivated on media containing lactic acid. Many experimenters have tried to verify these observations, but without success (P. Zeyland, A. Saenz, de Sanctis Monaldy, Bruno Lange, Ludwig Lange, Aldershoff, William H. Park and his coworkers). And Sasano and Medlar's experiments have been refuted by those of A. Boquet and of William H. Park.

Accordingly, *nobody has ever really succeeded in rendering BCG virulent,*[4] though it has been cultivated on every imaginable medium and though the animals inoculated with *BCG* have been submitted to all sorts of treatment, to diminish their resistance against tuberculosis (secondary infections, intoxications by different toxins or poisons, hunger, avitaminosis, low temperature, animal passages by different inoculation modes, such as subcutaneous, intraperitoneal, intracerebral, testicular, ocular, etc.).

Perhaps in the future some laboratory artifice will be discovered, that will permit one to gradually restore the virulence this strain possessed 23 years ago, before its characters had been modified by us by 230 successive cultures on pure ox-bile (432 to-day). But, even if such a return to virulence should be artificially obtained some day, that would not change the fact, advocated by us to-day, that *BCG, as it is used for infants and bovine vaccination, is a fixed, attenuated virus,* causing always the same curable lesions which it is impossible to reproduce by animal passages, when it is inoculated into the peritoneum of guinea pigs or into the anterior chamber of the rabbit's eye. It has always the same antigenic properties *in vitro* and *in vivo,* the same cultural characteristics, and the same aptitude to immunize the receptive organism against virulent superinfections.

[4] A. Calmette and C. Guerin, Boquet, Negre, J. Valtis, A. Saenz, de S. Monaldi, Tzeknowitzer, E. Dreyer, Elbert and Gelberg, G. Blanc, Fujioka, Leuret and Caussimon, Ranicovitz, Blumenberg, Jensen, Lange and Clauberg, B. Lange and Lydtin, Buschmann, Mouriquand and Bertoye, Balozet, P. Zeyland, Nasta and Catzap, de Assis, Mauriac and Aubertin, Aldershoff, Ascoli, Chagas, S. Griffith, Igersheimer and Schlossberger, William H. Park, J. Troisier, J. Boquien and de S. Monaldi, etc.

PROTECTION AGAINST TUBERCULOSIS WITH BCG IN GUINEA PIGS[1]

KONRAD E. BIRKHAUG

That the movement has gained a new and significant impetus in recent years to increase man's resistance against tuberculous infection by means of artificial tuberculization is indisputable. The credit for this added interest is mainly due to the development of *BCG* (*Bacillus Calmette-Guérin*), whose virulence is so low that even in large doses it is incapable of producing progressive tuberculosis when administered enterally or parenterally. Much evidence is already available that as a vaccine the *BCG* is capable of arousing an effective immunity response in both animals and man, either partly or wholly, to ward off an attack of virulent disease. Such were the claims originally made for the *BCG* by Professor Calmette and his colleagues at the Pasteur Institute. Not only in France and her colonies, but throughout the world, extensive experiments are in progress to appraise the full value of *BCG* as a prophylactic measure against tuberculous infection. It is undeniable that the majority of investigators uphold Calmette's original thesis of the harmlessness of *BCG* vaccination. On the other hand, a few opponents have voiced their belief that the *BCG* culture is not wholly avirulent, but that it is capable occasionally of producing progressive and fatal tuberculosis. One notes with interest that most workers claiming virulence for *BCG* resort to experimental artifices which deviate from Calmette's method of culturing the *BCG*. Such artifices include the cultivation of *BCG* on special media, in relative anaerobiosis, in pure culture or in combination with other virulent or avirulent organisms, and, again, in variant colonies dissociated from the original whole culture, such as smooth "S" and rough "R" strains. And, while the controversy continues to be waged between adherents and opponents of Calmette's contention of the harmlessness of *BCG* as a vaccine, over one million infants and numerous adults have been subjected to vaccination with this living organism. It is needless to stress the utmost importance of continued investigation of the fixity of

[1] From the Department of Bacteriology, University of Rochester School of Medicine and Dentistry, Rochester, New York.

this strain of tubercle bacillus until the proof of its reputed avirulence has been adequately presented by laboratory workers everywhere and by experiments conducted along entirely different lines. It is true that sharp criticism has been voiced in some quarters against the conservative attitude assumed by English and American investigators who maintain that the extensive use of *BCG* in human beings is unjustifiable on the ground that this culture is not a fixed virus and may mutate to become dangerous. A passionate analysis of this attitude has been given by Petroff (1), who frankly anticipates a catastrophe to happen by the continued use of *BCG*. The soundness of this conservative stand is beyond question when human lives are concerned. But in spite of the Lübeck tragedy which needs must be ascribed to neglect in certain important precautions, as was reflected in the verdict rendered by the Superior Court at Lübeck, no cause for great alarm has been occasioned by the universal use of *BCG* in over one million persons.

Some justification exists for the use of a living organism such as *BCG*, inasmuch as the employment of dead tubercle bacilli for the prevention of tuberculosis has never yielded results sufficient to make such vaccinations popular. Of late the belief is growing among medical experts that only the living attenuated tubercle bacilli can stimulate adequate resistance with which to ward off virulent infection. The popularity of *BCG* is directly attributable to this belief. But whether or not vaccination with *BCG* will continue to meet with universal approval must depend largely upon irrefutable proof that the vaccine is harmless.

The present study was undertaken three years ago because of existing conflicts in experimental data and difference of opinion that *BCG* is capable of arousing an effective immunity response against virulent disease. The questions I have essayed to answer in the following experiments are these: (1) Is the *BCG* culture avirulent and incapable of producing progressive tuberculosis in guinea pigs? (2) Is *BCG* capable of arousing an allergic response in newly-born or adult guinea pigs vaccinated enterally or parenterally? (3) Is the degree and duration of cutaneous allergy related to resistance to superimposed virulent infection? (4) Do cultures of dissociated smooth "S" colonies of *BCG* produce progressive tuberculosis in guinea pigs as claimed by Petroff and his colleagues (6)? Finally, (5) does the cultivation of *BCG* in deep broth cultures restore the original virulence of the culture as claimed by Dreyer and Vollum (2)? An enormous literature has accumulated, which answers most of these questions, since this study was undertaken. It is

felt, however, that much more confirmatory evidence of the validity of claims made for *BCG* vaccination is highly desirable.

EXPERIMENTAL

Tuberculinogenic Principle of BCG Whole and Dissociated Cultures: Three strains of *BCG* were employed in these studies: *BCG* Park no. 10, *BCG* Rockefeller no. 9 and *BCG* Pasteur no. 420–32, generously sent me by Drs. William H. Park, Florence R. Sabin and A. Calmette. No appreciable difference existed between these strains morphologically or culturally. Monthly transfers were made on Dorset's glycerine-egg, Calmette's glycerine-bile-potato, glycerine-potato and Sauton's synthetic medium. Extreme care has been taken to keep these cultures separate from virulent acid-fast organisms. During the past year all *BCG* material was kept in a separate room accessible only to me and with the double precaution of placing a padlock on the incubator. Although Calmette has advocated the sole use of glycerine-bile-potato, glycerine-potato and Sauton's synthetic medium for the cultivation of *BCG*, I have carried the Park and Rockefeller strains on Dorset's glycerine-egg medium for 3 years without having observed any enhancement of virulence. Dissociation of *BCG* into "R" and "S" colonies was accomplished by allowing the emulsified and paper-filtered suspension to flow over the surface of 20 petri plates containing Petroff's gentian-violet-egg medium. These plates were sealed with rubber bands and incubated at 37°C. from 3 to 8 weeks. Only a few "S" colonies were available, and these were transferred to slants of Petroff's gentian-violet medium for further cultivation. The "R" colonies which predominated on all the plates were treated similarly. Eventually these cultures were floated on Sauton's synthetic medium and 5 per cent glycerinated broth for the production of tuberculin. Whole cultures of *BCG* and the virulent strains of H37 and "Bovine Vallee" were also floated on Sauton's synthetic medium and 5 per cent glycerinated broth for the production of tuberculin. These cultures were grown for 6 weeks. At that time the entire culture was heated on the water-bath at a temperature varying between 80° and 90°C. until reduced to one-tenth the original volume. Final filtration took place through a Berkefeld N candle. A 5 per cent solution of tuberculin was always prepared in saline solution shortly before use and a standard dose of 0.1 cc. was always injected intracutaneously. The maximum diameters of redness observed 48 hours after injection of the tuberculin were recorded. Table 1 shows the tuberculin reactions in tuberculous

guinea pigs tested simultaneously with tuberculins produced by the 3 *BCG* cultures and the virulent H37 and "Bovine Vallee." It will be noted that no striking difference exists in the cutaneous reactions elicited with these various tuberculins. Table 2 also shows that little or no differ-

TABLE 1

*Tuberculin reactions in tuberculous guinea pigs tested simultaneously with tuberculins produced by BCG strains and virulent cultures**

GUINEA-PIG NUMBER	INTRACUTANEOUS INJECTION OF 0.1 CC. OF 5 PER CENT TUBERCULIN PRODUCED BY				
	Virulent strains of		Avirulent strains of		
	Human H37	Bovine "Vallee"	BCG Park No. 10	BCG Rockefeller No. 9	BCG Pasteur No. 420–32
	mm.	*mm.*	*mm.*	*mm.*	*mm.*
14	15 × 18	12 × 16	12 × 18	12 × 16	12 × 18
42	14 × 20	12 × 18	14 × 16	14 × 18	12 × 18
493	15 × 22	16 × 25	18 × 22	16 × 22	20 × 24
495	16 × 20	16 × 22	12 × 20	14 × 18	16 × 22

* Maximum diameters of redness 48 hours after injection.

TABLE 2

*Tuberculin reactions in tuberculous guinea pigs tested simultaneously with tuberculins produced by (1) rough "R," (2) smooth "S" and (3) whole BCG cultures**

GUINEA-PIG NUMBER	INTRACUTANEOUS INJECTION OF 0.1 CC. OF 5 PER CENT TUBERCULIN PRODUCED BY BCG PARK NO. 10		
	Rough "R" strain	Smooth "S" strain	Whole culture
	mm.	*mm.*	*mm.*
416	14 × 14	14 × 16	14 × 14
441	9 × 9	10 × 10	12 × 12
449	15 × 15	15 × 15	17 × 19
435	15 × 15	13 × 14	14 × 14
448	10 × 12	10 × 10	12 × 14
446	15 × 15	15 × 15	13 × 15
450	10 × 10	8 × 10	11 × 12
445	14 × 14	11 × 12	11 × 14
425	12 × 12	12 × 14	12 × 14
431	10 × 10	10 × 10	10 × 12

* Maximum diameters of redness 48 hours after injection.

ence obtains in the cutaneous reactions elicited in tuberculous guinea pigs injected simultaneously with tuberculins produced by the whole *BCG* culture or its variant "R" and "S" colonies and that these reactions compare well with those obtained by tuberculins produced by virulent

strains of tubercle bacilli. Inasmuch as it is generally believed that cutaneous allergy is a definite expression of immunity against virulent tuberculous infection, it is interesting to know that the *BCG* cultures employed universally for immunization against tuberculous disease contain the same tuberculinogenic principle as that possessed by cultures of virulent tubercle bacilli.

IMMUNITY EXPERIMENTS WITH BCG ON GUINEA PIGS

1: Resistance of Orally BCG-Vaccinated Newly-Born Guinea Pigs to Virulent Tuberculous Superinfection: Ten newly-born and tuberculin-negative guinea pigs, weighing on the average 80 gm., were fed 10 mgm. (dry weight) of a 4-weeks culture of *BCG* Park no. 10 from a pipette. During the first 4 days acid-fast organisms were recovered from the faeces in abundance, both in smears and in cultures prepared by Corper's method on gentian-violet-potato. The passage of acid-fast organisms in the faeces rapidly diminished until no organisms were found in 7 guinea pigs on the sixth day. A few organisms persisted in the faeces in 1 guinea pig until the ninth day and in the remaining 2 animals until the thirteenth and fifteenth days respectively. Diarrhoea developed in 3 guinea pigs on the day following the feeding of *BCG*, but cleared up promptly during the next 2 days. Intracutaneous tuberculin tests were performed at biweekly intervals with 0.1 cc. of a 5 per cent solution of bovine Old Tuberculin (Mulford) and the reading of the reaction was taken 48 hours after the intracutaneous injection. The first positive reaction occurred 15 weeks after the *BCG* feeding in 2 guinea pigs; in 19 weeks 4 out of 10 guinea pigs gave positive tuberculin reactions. During an interim of 6 months following the oral administration of 10 mgm. of *BCG* no indications of tuberculous infection were noted in any of these animals and the average weight had increased from 80 to 342 gm.

Six months after the feeding of *BCG* approximately 100 virulent and living H37 tubercle bacilli were injected subcutaneously into the right inguinal region in the 10 vaccinated and 10 control guinea pigs of about the same weight and age as the vaccinated animals. No immediate allergic manifestations were observed in any one of the vaccinated guinea pigs at the site of inoculation. The curves of average weight, tuberculin sensitivity and period of survival of the vaccinated and control groups of guinea pigs are shown in chart 1. It will be noted that 60 per cent of both groups became strongly tuberculin-positive within 3 weeks following the virulent superinfection and that, 2 weeks afterward, 100 per cent of

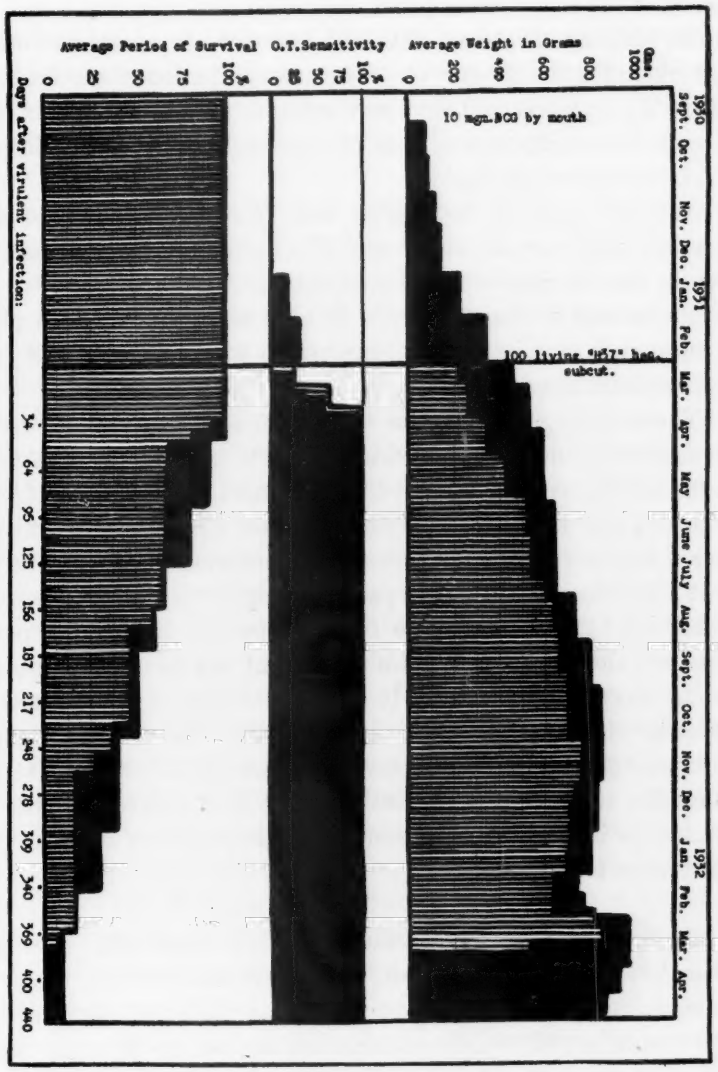

Average Period of Survival
O.T. Sensitivity
Average Weight in Grams
Gms. 1000
800
600
400
200
0
10 mgm. BCG by mouth
100 living "H37" bac. subcut.
1930
Sept. Oct. Nov. Dec. 1931 Jan. Feb. Mar. Apr. May June July Aug. Sept. Oct. Nov. Dec. 1932 Jan. Feb. Mar. Apr.
Days after virulent infection:
54 64 95 125 156 187 217 248 278 309 340 369 400 440

CHART 1. Oral administration of 10 mgm. BCG culture in newly-born guinea pigs and results of subsequent subcutaneous injection with 100 living H37 virulent tubercle bacilli (20 animals). Black color—protected animals; vertical lines—controls.

both groups showed positive tuberculin reactions. The tuberculin test was repeated at monthly intervals and remained solidly positive until death of the animal took place.

No striking difference obtained between the vaccinated and control groups in the weight curves. The average period of survival of the vaccinated group was 220 days as compared with 197 days for the control group. The difference of only 23 days in favor of the vaccinated guinea pigs would seem negligible.

Autopsy material, both gross and microscopic, failed to reveal any marked difference, in degree and distribution of tuberculous lesions, between the vaccinated and control groups. It would appear, therefore, that the oral administration of *BCG* in newly-born guinea pigs fails to arouse sufficient immunity response to ward off fatal and progressive tuberculous disease.

These findings of irregular tuberculin sensitization and no increased resistance to superimposed virulent infection are readily explained by the experiments recently reported by Wethmar and Brunzema (3) and Griffith (4), who found that only a very small proportion of orally administered *BCG* organisms were capable to penetrate the mucous membrane of the alimentary tract and to pass the neighboring lymph nodes to set up localized tuberculosis. The results reported, it would appear, do not support the contention of Calmette that the mucous membrane of the alimentary canal of the newly-born guinea pigs is more permeable to the passage of *BCG* than that of older animals. Further study of parenteral administration of *BCG*, which will be discussed below, definitely indicates that the enteral mode of administering *BCG* yields the most uncertain results in increasing an animal's resistance to superimposed virulent tuberculous infection.

2: Resistance of Intraperitoneally BCG-Vaccinated Guinea Pigs to Virulent Tuberculous Superinfection: Ten normal and tuberculin-negative guinea pigs, weighing on the average 580 gm., were injected intraperitoneally with a saline suspension containing 20 mgm. (dry weight) of a 4-weeks culture of *BCG* Park no. 10. No immediate and unfavorable symptoms and signs developed following the inoculation. Intracutaneous tuberculin tests were performed at biweekly intervals with 0.1 cc. of a 5 per cent solution of bovine Old Tuberculin (Mulford) and the readings made 48 hours later. Within 2 weeks 30 per cent gave positive tuberculin tests, within 4 weeks 50 per cent, within 6 weeks 80 per cent

and from 8 to 10 weeks 100 per cent. Cutaneous allergy began to decline at this time and 12 weeks after the intraperitoneal *BCG* inoculation 60 per cent gave positive tuberculin tests, within 14 weeks 10 per cent and when tested, within 16 to 18 weeks, all the animals gave negative tests.

During the interim of 18 weeks following the *BCG* inoculation, the average weight of the vaccinated group had risen from 580 to 724 gm., a net gain of 160 gm. During this period no deaths had occurred as a result of the vaccination.

Development of abscesses and ulcers, either at the site of inoculation or in the scrotal sac, occurred between 2 and 3 weeks after the intraperitoneal *BCG* inoculation in 4 guinea pigs. The thick creamy caseopurulent discharge contained numerous acid-fast organisms in smears and profuse growth of typical tubercle bacilli took place on Corper's gentian-violet-potato when the material was streaked across its surface and the tubes incubated from 3 to 10 weeks at 37°C. Part of the caseopurulent discharge was injected subcutaneously in 5 normal and adult guinea pigs. These were autopsied after 8 to 10 weeks without revealing tubercles anywhere in the body except in the adjacent inguinal lymph nodes where the purulent material was injected. As a rule, a localized swelling took place at the site of injection, in the course of 2 weeks after inoculation, which gradually softened, ulcerated and formed a discharging abscess. The adjacent lymph nodes always participated in the swelling, although they never ulcerated through the skin nor became adherent to it. The ulcers and abscesses usually healed promptly within 4 to 6 weeks and the only trace of the process was a white scar in the overlying skin.

Nineteen weeks after the intraperitoneal *BCG* inoculation, approximately 200 living and virulent H37 tubercle bacilli were injected subcutaneously in the right inguinal region in the 10 vaccinated guinea pigs. A group of 30 normal and tuberculin-negative guinea pigs, of approximately the same age as the vaccinated animals, was likewise injected with about 200 living and virulent H37 tubercle bacilli. These 30 animals will serve the purpose of control for the 3 groups of parenterally vaccinated guinea pigs and the results reported will represent the average mean of body weight, tuberculin sensitivity and period of survival for the entire group.

Localized redness and swelling, at the site of the subcutaneous injection of the virulent tubercle bacilli, developed promptly in all the *BCG*-vaccinated animals. It is interesting to note the occurrence of this typical allergic reaction in the absence of cutaneous allergy to Old Tubercu-

lin. This allergic reaction persisted for 4 days. No similar reactions were observed in the control series. Development of an abscess at the site of the subcutaneous inoculation occurred in 3 vaccinated guinea pigs in the third week after the virulent superinfection. The creamy caseopurulent discharge contained many acid-fast organisms in smears. The process healed rapidly and cicatrized completely, leaving only a white scar in the skin. The remaining 7 vaccinated guinea pigs developed slightly enlarged inguinal lymph nodes in the neighborhood of the virulent infection. The nodes became stationary in size and failed in every instance to lead to ulceration through the overlying skin. No distressing symptoms or signs of progressive tuberculous disease developed in the *BCG*-vaccinated group until 200 days after the virulent superinfection had taken place. During this interim the average weight of this group had risen to 900 gm., or a net gain of 176 gm. since inoculation with virulent tubercle bacilli, while the control group showed a slightly lower gain in weight, namely 158 gm. The curves of average weight, tuberculin sensitivity and period of survival are shown in chart 2.

If the hypothesis is true that tuberculoimmunity is a function of tissue allergy by which the defense mechanism of the immune body is accelerated and exaggerated in the attempt to hem in the bacilli of superinfection and by this allergic reaction to interfere with the migration of the virulent organisms to other parts of the body, then new light will be shed upon this hypothesis by correlating the curves of cutaneous allergy obtainable in the *BCG*-vaccinated guinea pigs and the control nonvaccinated animals. Thus it will be noted that 90 per cent of the intraperitoneally *BCG*-vaccinated guinea pigs became tuberculin-positive 3 weeks after the virulent superinfection and that the reactions rapidly declined to 40 per cent in 4 weeks, 20 per cent in 8 weeks and 10 per cent in 10 weeks. The tuberculin sensitivity remained at this low level for 24 weeks and gradually began to rise in direct proportion with development of symptoms and signs of a progressive and fatal tuberculous infection. In contrast with this sudden rise and fall and gradual rise in tuberculin sensitivity, it will be noted that the control nonvaccinated animals became tuberculin-sensitive simultaneously with the vaccinated animals, but that the curve of positive reactors remained solidly straight after having once become 100 per cent positive. It would thus appear that the allergic "barrier," so impressively demonstrated by Krause and Willis (5), is readily stimulated into action by the *BCG* vaccination and that the visible ultimate consequence is the appearance of delayed, abortive or

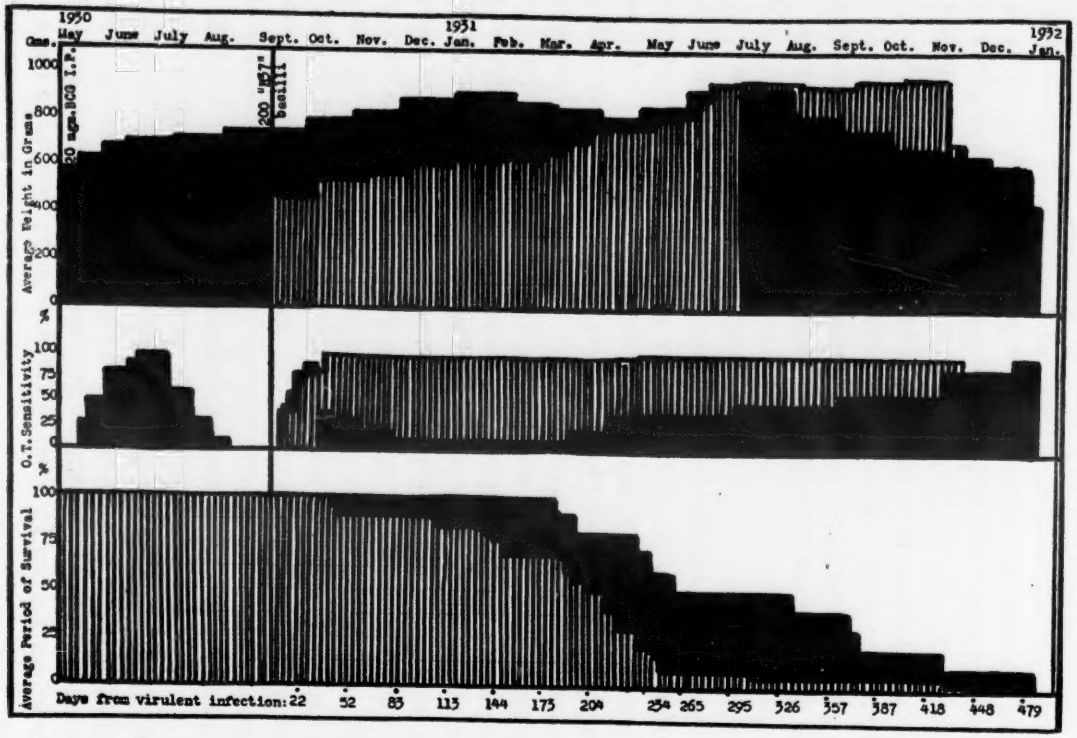


CHART 2. Intraperitoneal injection of 20 mgm. BCG culture in young guinea pigs and results of subsequent subcutaneous injection with 200 living H37 virulent tubercle bacilli (10 protected animals and 30 controls). Black color—protected animals; vertical lines—controls.

more chronic disease. This is clearly demonstrable in the curves of period of survival of the *BCG*-vaccinated and the nonvaccinated animals. Here we find that the average period of survival of the vaccinated group was 304 days, as contrasted with 189 days for the control group. The mean difference of 115 days in favor of the vaccinated animals is significant. The earliest death among the vaccinated group took place 177 days after the virulent superinfection, while the first control animal died 38 days after injection of the virulent tubercle bacilli.

Autopsy material, both gross and macroscopic, demonstrated that the vaccinating dose of 20 mgm. of *BCG* had produced a thickening of the omentum, with numerous bands and points of fibrous tissue interconnecting the omentum with the stomach, folds of intestine, the parietes and the viscera. Otherwise, no evidence was obtained, at this late date after the intraperitoneal injection of the *BCG*, that the tuberculous lesions, which led to the death of the vaccinated group, differed in degree or distribution from those occurring in the control group. These findings are in accord with the extensive and thorough-going experiments of Krause and Willis (5), who came to the conclusion that, in conducting immunity studies, the animals should be killed several months after the superimposed virulent infection, in order properly to appraise the immunity response of the vaccinated animals. Ordinarily, the immune guinea pigs will never have died of tuberculosis as early as 3 to 4 months after the virulent superinfection, while the nonimmunes develop visceral and fatal tuberculosis by this time.

3: Resistance of Subcutaneously BCG-Vaccinated Guinea Pigs to Virulent Tuberculous Superinfection: Ten normal and tuberculin-negative guinea pigs, weighing on the average 385 gm., were injected subcutaneously in the right inguinal area with a saline suspension containing 20 mgm. (dry weight) of a 4-weeks culture of *BCG* Park no. 10. The area injected showed increasing tumefaction after 10 days and within 16 days the overlying skin became deeply red, swollen and firm. A softening process took place during the third week and this led to ulceration of the skin and abscess-formation. A creamy caseopurulent material discharged from the abscess. Numerous acid-fast organisms were seen in the smears of this material and the organism was recovered in culture on Corper's gentian-violet-potato. Subsequent subcutaneous inoculation of this material into 3 normal guinea pigs led to a repetition of the abscess-formation, rapid healing and formation of scar-tissue. When these animals were

sacrificed 8 to 10 weeks later no trace of visceral tuberculosis was found, and the regional lymph nodes showed increased fibrous-tissue formation surrounding central masses of caseous material. All the abscesses of the subcutaneously *BCG*-vaccinated guinea pigs healed and cicatrized completely within 2 to 3 months after the inoculation. Adjacent inguinal lymph nodes became slightly swollen along the tenth day after inoculation. In no instance was ulceration or abscess-formation of the lymph nodes noted. No symptoms or signs of tuberculous disease developed in any one animal during the first 17 weeks after the inoculation. The group had made an average net gain in weight of 325 gm. during this period.

The biweekly tuberculin tests showed the following results: 10 per cent of the animals became tuberculin-positive 2 weeks after the subcutaneous *BCG* inoculation, 30 per cent in 4 weeks, and 100 per cent between 6 and 14 weeks. At this time a decline in positive reactions was noted and only 50 per cent gave positive tests in 16 weeks, and in 17 weeks the entire group gave negative reactions.

During the anergic phase, which occurred in the seventeenth week following the subcutaneous *BCG* vaccination, approximately 200 living and virulent H37 tubercle bacilli were injected subcutaneously in the left inguinal region in the 10 vaccinated guinea pigs. The control group, treated similarly, has already been described elsewhere. The injected area became greatly swollen, red and soft within 24 hours. This allergic phenomenon persisted for 4 days when the process promptly subsided. Two weeks after the virulent superinfection, a marked local tumefaction occurred at the site inoculated 19 weeks previously with 20 mgm. of *BCG*. This delayed allergic reaction was observed in every one of the 10 vaccinated guinea pigs. The swollen areas became soft and deeply injected. No ulceration took place to the surface and the inflammatory process cleared up after 4 to 6 days.

Seven guinea pigs developed an abscess at the site of the virulent superinfection 3 weeks after inoculation. Smears made of the creamy caseopurulent discharge revealed numerous acid-fast organisms. These processes promptly healed and completely cicatrized, until only delicate white scars indicated the previous site of the abscesses. For about 6 weeks following the injection of virulent tubercle bacilli, the regional lymph nodes became slightly enlarged, but remained stationary in size and failed to ulcerate to the surface. No symptoms or signs of tuberculous disease were noticeable during 200 days after the virulent superin-

fection. During this interim, the average weight curve showed a gain of 190 gm. A gradual decline in the individual weight and general health became apparent about 32 weeks after the virulent superinfection.

Tuberculin reactions presented the identical sudden rise and fall and subsequent delayed rise following the virulent superinfection as was already described in the animals injected intraperitoneally with *BCG* and later infected with virulent tubercle bacilli. Seventy per cent became positive with tuberculin 1 week after the virulent superinfection, 100 per cent within 4 weeks, with a drop to 30 per cent within 8 weeks and to 20 per cent from 9 to 20 weeks. A slow rise was observed to take place about 50 weeks after the virulent superinfection, when 60 per cent of the guinea pigs became tuberculin-positive and within 65 weeks all the surviving animals gave positive reactions. One notes with interest that the re-occurrence of positive tuberculin tests is concomitant with ominous symptoms and signs of progressive tuberculous disease and *exitus*.

The average period of survival was 340 days for the subcutaneously *BCG*-vaccinated animals as contrasted with 189 days for the nonvaccinated controls. The mean difference in longevity of 151, plus 1 surviving animal, is decidedly in favor of the subcutaneous mode of *BCG* vaccination. The earliest death among the vaccinated animals took place 151 days after the virulent superinfection, while the first control animal died 38 days after an identical virulent superinfection.

Autopsy material, both gross and microscopic, showed extensive tuberculous lesions throughout thoracic and abdominal organs, with heavy involvement of the lymph nodes. Both in degree and distribution of tuberculous lesions it was difficult to detect any appreciable difference (at this late date after *BCG* vaccination) between the vaccinated and control groups.

The outstanding and significant feature of *BCG* tuberculoimmunity in guinea pigs, of retarding the spread of virulent tubercle bacilli within the body, is strikingly exemplified in the following experiment. Guinea pig no. 93, subcutaneously vaccinated with 20 mgm. of *BCG*, succumbed to visceral tuberculosis 445 days after the virulent superinfection with approximately 200 H37 tubercle bacilli. At autopsy, a caseous mesenteric lymph node was excised, macerated and emulsified in saline solution. By direct count it was estimated that 0.1 cc. of this emulsion contained approximately 200 acid-fast organisms. This dose was injected subcutaneously in the right inguinal region. The guinea pig succumbed with extensive visceral and pulmonary tuberculosis 52 days after the inocula-

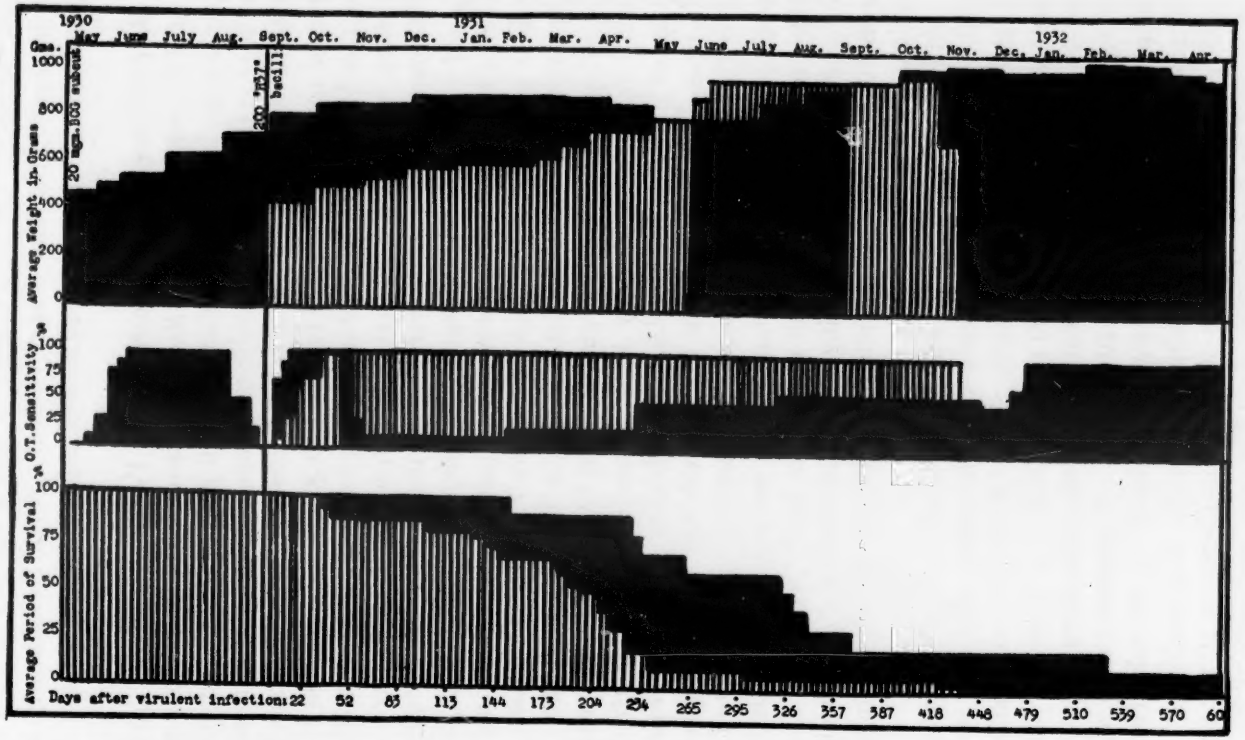


CHART 3. Subcutaneous injection of 20 mgm. BCG culture in young guinea pigs and results of subsequent subcutaneous injection with 200 living H37 virulent tubercle bacilli (10 protected animals and 30 controls). Black color—protected animals; vertical lines—controls.

tion. In short, the *BCG*-vaccinated guinea pig was capable to resist approximately the same dose of virulent tubercle bacilli nearly 400 days longer than the nonvaccinated control animal.

4: Resistance of Intracutaneously BCG-Vaccinated Guinea Pigs to Virulent Tuberculous Superinfection: Ten normal and tuberculin-negative guinea pigs, weighing on the average 520 gm., were injected intracutaneously, in the skin overlying the right inguinal region, with a saline suspension containing 20 mgm. of a 4-weeks culture of *BCG* Park no. 10. An intense redness and marked tumefaction occurred 3 days later at the site of injection. The inflammatory process led to the production of a small abscess, about 5 to 8 mm. in diameter, about the fifth day. A thick caseopurulent material discharged from the abscess. This material contained numerous acid-fast organisms, which were recovered in culture on Corper's gentian-violet-potato. Subsequent reinoculation into normal guinea pigs failed to produce progressive tuberculous disease. During the second week after the intracutaneous inoculation of *BCG*, the surrounding skin began to desquamate, and haemorrhage was readily produced from the abscess by light pressure. Slight enlargement took place of adjacent lymph nodes. These became stationary in size and at no time produced ulceration to the overlying skin. The abscess produced at the site of *BCG* inoculation continued to suppurate for 5 to 6 weeks, at which time the wound healed and completely cicatrized. At this time the regional lymph nodes were hardly palpable. During the interim of 16 weeks following the intracutaneous *BCG* inoculation no symptoms or signs of tuberculosis developed and the average gain in weight was 230 gm.

Biweekly tuberculin tests with 0.1 cc. of a 5 per cent solution of bovine Old Tuberculin (Mulford) showed the following reactions: 50 per cent of the animals reacted positively within 3 weeks after vaccination, 90 per cent within 5 weeks and 100 per cent from 6 to 16 weeks. Seventeen weeks after the *BCG* vaccination the cutaneous allergy dropped to 50 per cent and in 18 weeks to 20 per cent. It appears, therefore, that the more durable cutaneous allergy is produced by the subcutaneous and intracutaneous methods of administering the *BCG* vaccine.

During the anergic phase of cutaneous allergy in 80 per cent of the vaccinated animals, approximately 200 living and virulent H37 tubercle bacilli were injected subcutaneously in the left inguinal region in all 10 animals. The control series of 30 guinea pigs, similarly injected, has

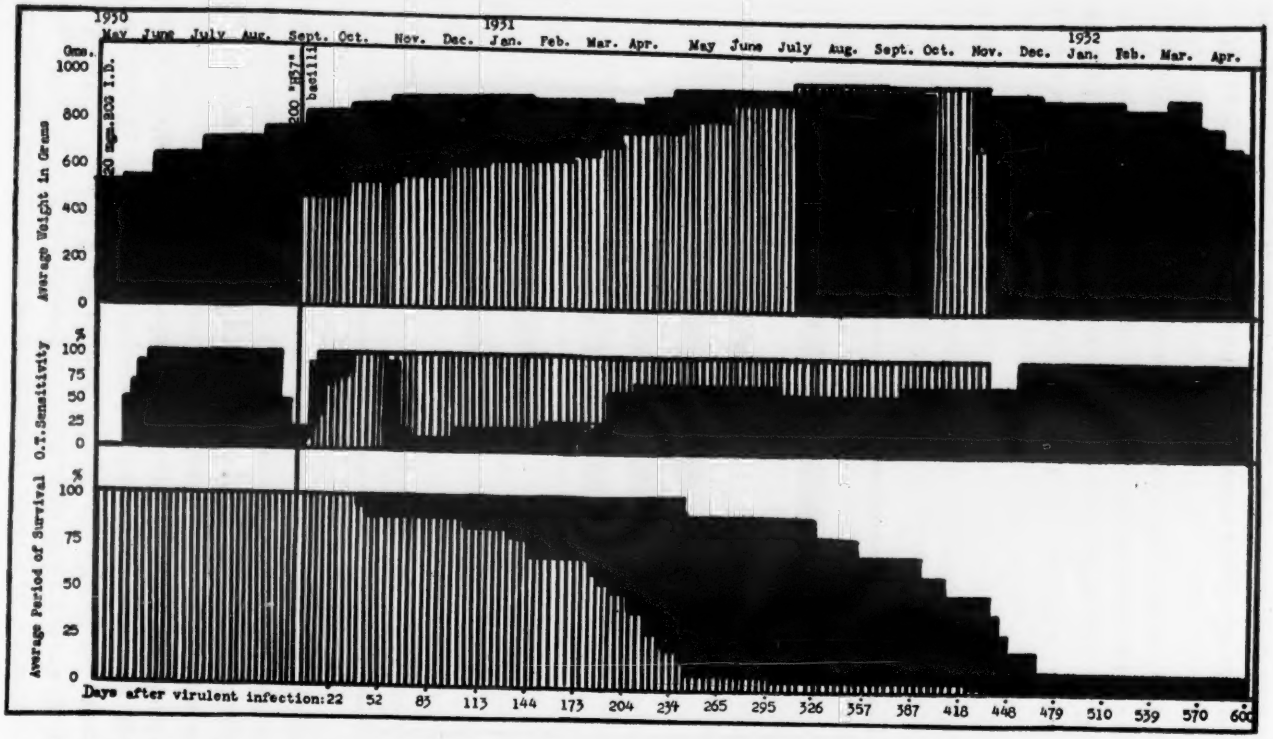


CHART 4. Intracutaneous injection of 20 mgm. BCG culture in young guinea pigs and results of subsequent subcutaneous injection with 200 living H37 virulent tubercle bacilli (10 protected animals and 30 controls). Black color—protected animals; vertical lines—controls.

already been described under the intraperitoneally *BCG*-vaccinated animals. Within 24 hours after the virulent superinfection, all the animals displayed the typical Koch phenomenon at the site of the injected tubercle bacilli. The deeply injected, soft and swollen area gradually diminished during the following 5 days and no trace remained after 6 days. The regional lymph nodes participated in the inflammatory reaction and became slightly enlarged. The peculiar delayed allergic reaction described above under the intraperitoneally and subcutaneously *BCG*-inoculated guinea pigs, was also observed in the intracutaneously

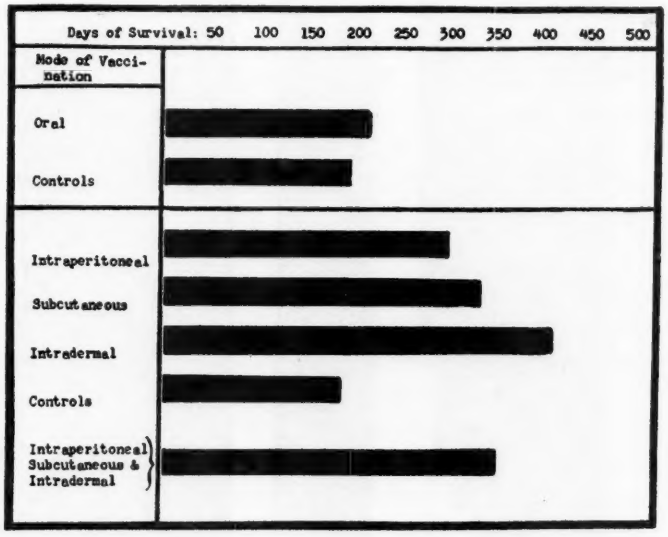


CHART 5. Average duration of life of guinea pigs vaccinated by various routes with 10 to 20 mgm. BCG culture and subsequently inoculated subcutaneously with 100 to 200 living H37 virulent tubercle bacilli (80 animals).

BCG-vaccinated animals. During the third week after the virulent superinfection, the area injected 20 weeks previously with *BCG* suddenly became inflamed and swollen. The reaction promptly subsided within 1 week without producing pigmentation or desquamation in the overlying skin.

Discharging abscesses developed in 4 guinea pigs in the areas inoculated with the virulent H37 tubercle bacilli. Numerous acid-fast organisms were found in smears made. These abscesses occurred during the third and fourth weeks after the virulent superinfection and persisted for 4 to

6 weeks when they healed completely. During the following 240 days after superinfection, the right inguinal lymph nodes remained hardly palpable in all but 3 guinea pigs. During this interim no severe symptoms or signs of tuberculous disease were observed in the group of vaccinated guinea pigs and the average weight had increased 150 gm.

The curve of tuberculin sensitivity presented the identical sudden rise and fall and subsequent delayed rise following the virulent superinfection in the intracutaneously *BCG*-vaccinated animals as was described above under the intraperitoneally and subcutaneously *BCG*-vaccinated animals. Within 2 weeks after the superimposed infection, 100 per cent gave positive tuberculin tests and in 9 weeks only 20 per cent gave positive reactions while 10 per cent reacted within 11 weeks. The gradual rise in positive reactions followed closely the concomitant increase in symptoms and signs of progressive tuberculous disease.

In the series of intracutaneously *BCG*-vaccinated guinea pigs is encountered the most striking and suggestive tuberculoimmunity in retarding the fatal issue of virulent superinfection. It will be noted that the average period of survival of the vaccinated animals was 417 days following the virulent superinfection and 189 days for the nonvaccinated controls. This represents the significant difference in longevity of 229 days, plus 1 surviving animal, in favor of the intracutaneous mode of *BCG* vaccination.

Autopsy material was studied carefully both macroscopically and in sections. No appreciable difference was detected at this late date after the *BCG* vaccination between this group and the control material.

VIRULENCE TESTS WITH BCG IN GUINEA PIGS

1: Intraperitoneal Injection into Guinea Pigs of Dissociated Smooth "S" Colony Strain of BCG Culture: After some initial difficulty, Petroff, Branch and Steenken (6) were able to dissociate 2 distinct types of colonies of the *BCG* culture. The "R" or rough colony was found to grow rapidly on Calmette's glycerine-bile-potato medium and in small islands which were readily removed from the surface of the medium. These "R" colonies were not easily emulsifiable in saline solution. The "S" or smooth colonies were found to grow less rapidly and in a veil-like manner close to the surface of the medium. The "S" colonies were emulsified with ease in saline solution. These investigators also demonstrated that the "R" colony was only capable of producing a localized tubercle when injected parenterally into guinea pigs. The "S" colony,

on the other hand, was found occasionally to produce progressive and fatal tuberculosis in guinea pigs. It should be emphasized, however, that Petroff and his colleagues have not as yet been able to produce progressive tuberculosis in long series in guinea pigs injected parenterally with large doses of their "S" strain cultures dissociated from the original *BCG* culture. Petroff's claim for the occasional virulence of the whole *BCG* culture has been supported by Loewenstein (19), Galli-Valerio (20), Armengol (21), Watson (22), Chiari, Nobel and Solé (23), Korschun, Dwijkow and Gorochownikowa (24), Selter and Blumenberg (25), and Sasano and Medlar (26), while Kraus (27), Park (28) and Gerlach (29) more recently have changed their opinion about the virulence of the *BCG* culture. Although most investigators have been able to dissociate the *BCG* culture into typical "R" and "S" colonies, as described by Petroff and his colleagues, yet the claim of virulence for the "S" colony, as well as the whole *BCG* culture, has been emphatically denied by Neufeld (7), Bruno Lange (8), Gerlach (9), Prausnitz (10), Tzekhnovitzer (11), Park (12), Cantacuzène (13), Aldershoff (14), Saenz (17), and Boquet (18). The following is my own experience with the dissociated "S" colonies of the *BCG* Rockefeller no. 9 strain.

Dissociation of this strain was readily accomplished by emulsifying a 3-weeks culture, grown on Sauton's synthetic medium, in a sterile porcelain mortar. The even suspension of organisms was passed through a sterile Whatman no. 1 filter paper to remove any clumps of organisms. One drop of the filtrate was then allowed to run over the surface of Petroff's gentian-violet-egg medium. A rubber band was placed around the plate to prevent too rapid evaporation. Twenty plates were inoculated and incubated at 37°C. from 3 to 8 weeks. It was noted that the "R" colonies were predominant on all the plates and that only a few typical "S" colonies were available for subcultures. These colonies were picked and sown on slants of Dorset's and Petroff's media. The initial growth was exceedingly slow and corresponded in details to the observations made by Petroff and his colleagues. After several generations of subculturing, growth was accelerated, and eventually sufficient growth was available for massive inoculation of animals. Exactly 1 mgm. dry weight of the "S" colony strain was injected intraperitoneally into each of 10 normal and tuberculin-negative guinea pigs whose average weight was 300 gm. No immediate and unfavorable reactions were observed in any one of the inoculated guinea pigs. Chart 6 shows the curves of

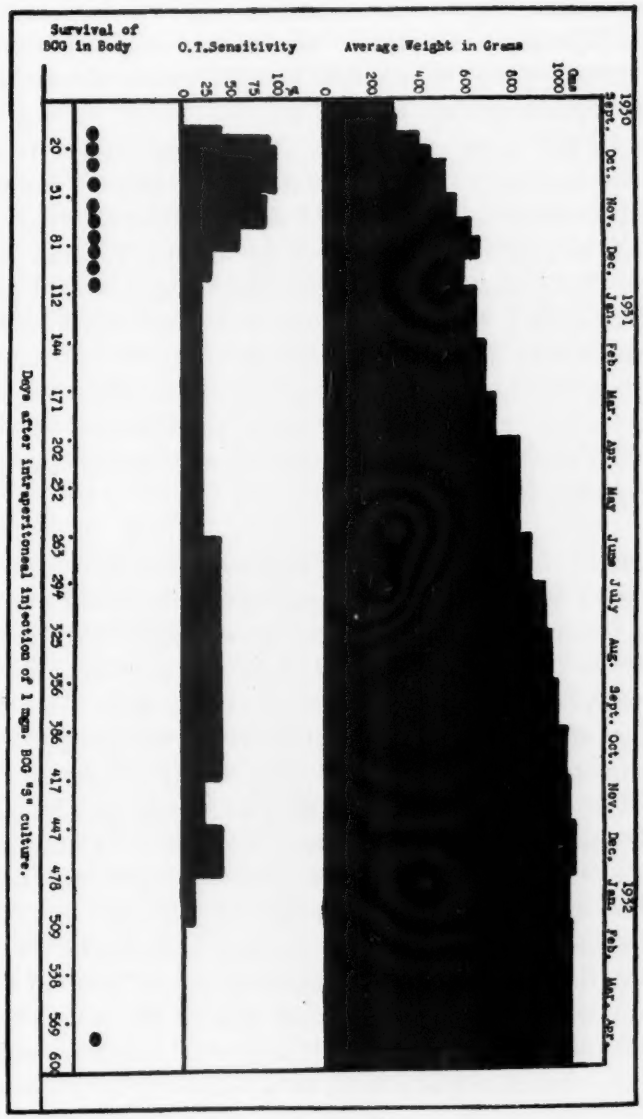


CHART 6. Intraperitoneal injection of 1 mgm. BCG "S" culture in young guinea pigs and results in weight, tuberculin skin reactivity and survival of *BCG* in body (10 animals).

average growth, tuberculin sensitivity and survival of *BCG* in the guinea pig body.

Nine guinea pigs are alive (June 17, 1932) 645 days after the intraperitoneal injection of 1 mgm. of "S" variant colonies of *BCG*. Guinea pig no. 143 died from intercurrent nontuberculous disease 577 days after the intraperitoneal injection of 1 mgm. of the "S" culture. The autopsy material will be discussed below. The average gain in weight has steadily risen from 300 to 1036 gm., or a net mean gain of 736 gm. The curve of tuberculin sensitivity with 0.1 cc. of a 5 per cent solution of bovine Old Tuberculin (Mulford) reads as follows: 3 weeks after the "S" colony inoculation 40 per cent of the animals reacted positively with tuberculin, in 5 weeks 100 per cent, in 9 weeks 80 per cent, in 12 weeks 60 per cent, in 14 weeks 30 per cent and from 16 to 36 weeks 20 per cent of the group gave positive tuberculin tests. For one year the curve wavered between 20 and 40 per cent of positive reactors and since January 15, 1932, tuberculin tests have been consistently negative in the surviving animals.

Survival of BCG in Guinea-Pig Body and Its Recovery in Culture: During the first 110 days after the intraperitoneal injection of 1 mgm. of the "S" variant colonies of *BCG*, 6 guinea pigs developed from time to time local abscesses in the abdominal wall at the site punctured during the intraperitoneal inoculation and also in the scrotal sacs. No other symptoms or signs of tuberculous infection occurred in this group of animals during an interim of nearly 2 years following the intraperitoneal "S" colony inoculation. The caseopurulent discharge from the abscesses was sown on Dorset's and Corper's media. Altogether 111 cultures were made and 38 of these tubes showed the presence of colonies of acid-fast organisms on the following days from the intraperitoneal inoculation with the "S" colony culture: 14, 20, 35, 41, 60, 64, 71, 78, 82, 96 and 109 days. During this interim 14 normal guinea pigs were injected with the whole caseous material from these various animals and in no instance was progressive tuberculosis observed in the visceral or thoracic organs when the animals were sacrificed 8 to 10 weeks following the subcutaneous inoculation. The purulent lesions were always confined locally to the area adjacent to the inoculated site. In subcultures the caseous material was shown to contain predominantly "R" colonies, indicating that the "S" colonies injected previously had reverted rather early after inoculation into the guinea pig body.

Autopsy material of guinea pig no. 143 revealed that death was due to pneumonia. No tuberculous lesions were detected grossly or in microscopic sections in the abdominal or thoracic organs. Only 3 small mesenteric lymph nodes, the size of a pea, were found to be enlarged and on section to contain a small amount of greenish-yellow thick caseous material. Smears revealed numerous highly granular acid-fast organisms. The material from one lymph node was treated by Corper's method and sown on 5 tubes of gentian-violet-potato. Two of these tubes presented 1 and 6 colonies respectively of acid-fast organisms after 6 weeks' incubation at 37°C. The second lymph node was macerated in saline solution and the entire emulsion injected subcutaneously into a normal guinea pig weighing 456 gm. This animal was sacrificed 10 weeks later and showed 3 enlarged inguinal lymph nodes at the site of injection. On section these nodes showed well-formed tubercles, a few small areas of caseation and numerous epithelioid cells. A large amount of tuberculous fibrous tissue indicated that the tuberculous process was well controlled.

The longest period of survival of *BCG* in the guinea pig body was 103 days after inoculation, as recorded by Griffith (15), while Bruno Lange (16) failed to recover *BCG* in culture from an animal of any species 6 weeks after inoculation. My own cultivation experiments show that the *BCG* organism may survive in the guinea pig mesenteric lymph node as long as 577 days after inoculation without producing progressive tuberculosis. It would appear, therefore, that the "S" colony, dissociated from the whole *BCG* culture, is harmless when injected into guinea pigs.

2: Intraperitoneal Injection in Guinea Pigs of Deep Broth Cultures of BCG (Dreyer-Vollum Method): Dreyer and Vollum (2) recently reported that they had succeeded in enhancing the viru ence of *BCG* for guinea pigs and rabbits by culturing their 2 strains of *BCG* (nos. 1 and 359) in partial anaerobiosis on the bottom of flasks containing veal broth. This startling work was repeated without success by Saenz (17), whose experiments showed that *BCG* cultivated for several generations on the bottom of peptonized veal broth finally loses its vitality by progressive rarefaction of living elements, to become entirely sterile within 3 months after the first deep broth-culture implantation. In the following study an attempt was made to repeat the work of Dreyer and Vollum with the *BCG* Park no. 10 strain employed throughout my experiments. On January 13, 1931, litre flasks containing 500 cc. of beef infusion broth, pH 6.8, were seeded on the bottom with about 200 mgm., moist weight, of

a 4-weeks culture of *BCG* Park no. 10 grown on Sauton's synthetic medium. Care was taken to eliminate any surface growth. On February 26, the cultures were centrifugated, weighed and transferred to other flasks containing the same amount of beef-infusion broth. A small amount of the culture was seeded on Dorset's and Corper's media. Abundant growth took place in 4 weeks at 37°C. No appreciable increment in weight had taken place in the deep broth *BCG* cultures during the first cultivation of 44 days. On April 1, the second passage of deep broth *BCG* culture was centrifugated and weighed. No increment in weight

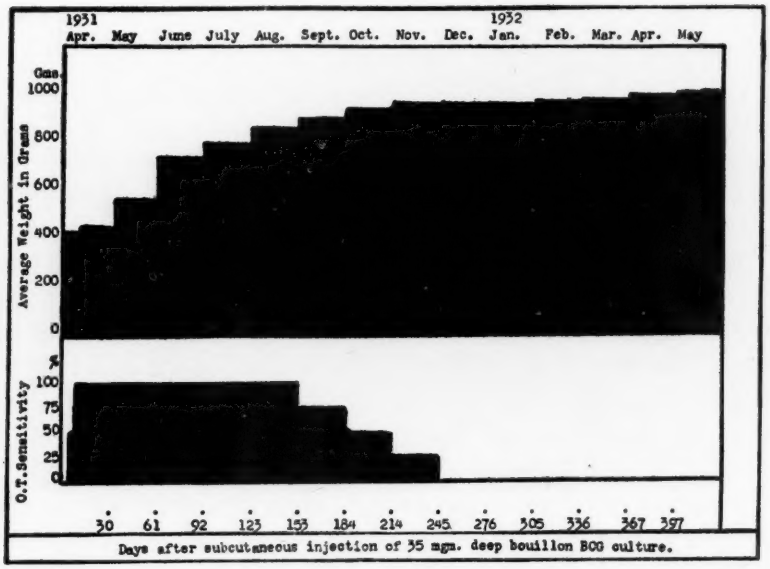


CHART 7. Subcutaneous injection of 35 mgm. deep bouillon *BCG* subculture, 56 days old (Dreyer and Vollum's method) (4 animals).

had occurred after 77 days of partial anaerobic cultivation of the *BCG* culture. A small amount of the culture was sown on 6 tubes of Dorset's and Corper's media. Four of these tubes remained sterile after 10 weeks' incubation while the remaining 2 tubes showed scant colony-formation. Four normal and tuberculin-negative guinea pigs, weighing on the average 408 gm., were each injected subcutaneously with 35 mgm., moist weight, of the second-passage deep broth culture of *BCG*. Chart 7 shows the curves of average weight and tuberculin sensitivity of these animals. During an interim of 440 days from the beginning of the ex-

periment, all the animals are alive and have made an average gain in weight of 511 gm. The tuberculin tests became 100 per cent positive 2 weeks after the *BCG* inoculation and remained solidly positive for 20 weeks. Thirty-two weeks after the *BCG* inoculation all the animals became anergic to tuberculin. The animals are in excellent health (June 16, 1932) and show no symptoms or signs of tuberculous disease. Thus it appears that *BCG* cultivated under partial anaerobiosis in deep broth cultures fails to show any increased virulence for guinea pigs. On the other hand, it is evident that *BCG* cultivated for several months under partial anaerobiosis, in deep broth cultures, loses its vitality, and, contrary to the claims of Dreyer and Vollum, is absolutely harmless when injected parenterally in guinea pigs.

SUMMARY

1. The tuberculinogenic principle of *BCG* is similar to that possessed by virulent bovine and human tubercle bacilli.

2. No appreciable difference obtains in tuberculous guinea pigs between the allergic cutaneous reactions elicited with tuberculins produced by virulent tubercle bacilli and *BCG*, whether whole or dissociated into "R" and "S" variant colony cultures.

3. The oral administration of *BCG* in newly-born guinea pigs fails to arouse regularly tuberculin sensitization or any increased resistance to virulent superinfection.

4. The parenteral administration of *BCG* in guinea pigs is capable of arousing localized tuberculous lesions which heal promptly without producing progressive tuberculous disease.

5. The parenteral *BCG* vaccination of guinea pigs produces regularly tuberculin sensitization and a significant tuberculoimmunity which is most marked in animals vaccinated intracutaneously and subcutaneously.

6. The parenterally *BCG*-vaccinated guinea pigs are relatively twice as refractory to progressive tuberculosis following virulent superinfection as the nonvaccinated animals.

7. Cultivation experiments demonstrate that *BCG* may survive in the body of the guinea pig as long as 577 days after inoculation without showing any tendency to produce progressive tuberculosis.

8. Parenteral administration in guinea pigs of large doses of the "S" smooth colony variant dissociated from *BCG* is capable of arousing localized tuberculous lesions which heal promptly without producing progressive tuberculosis.

9. *BCG* cultivated under partial anaerobiosis in deep broth cultures fails to show any increased virulence for guinea pigs, but rather loses its viability after several months' cultivation.

10. The experimental data presented indicate that *BCG* is harmless as a vaccine and is capable of arousing an outstanding and significant tuberculoimmunity when administered to guinea pigs by the parenteral routes.

Acknowledgments

The author is greatly indebted to Doctors Thomas B. Garlick and Robert I. Walter for assistance during the early part of the study and to Doctor William B. Hawkins, Assistant Professor of Pathology, for much practical assistance in looking over the postmortem material.

REFERENCES

(1) PETROFF, S. A.: Am. J. Publ. Health, 1928, xviii, 843; Amer. Rev. Tuberc., 1929, xx, 275; New England J. Med., 1932, ccvi, 436.
(2) DREYER, G., AND VOLLUM, R.: Lancet, 1931, i, 9.
(3) WETHMAR, R., AND BRUNZEMA, D.: Zeitschr. f. Hyg. u. Infekt., 1931, cxii, 332.
(4) GRIFFITH, A. S.: Medical Research Council, Special Report no. 152, 1931.
(5) KRAUSE, A. K., AND WILLIS, H. S.: A series of papers, Amer. Rev. Tuberc., 1926, xiv, 211–305.
(6) PETROFF, S. A., BRANCH, A., AND STEENKEN, W.: Proc. Soc. Exp. Biol. & Med., 1928, xxv, 14; Amer. Rev. Tuberc., 1929, xix, 9.
(7) NEUFELD, F.: Deutsche med. Wchnschr., 1930, lvi, 1599, & 2056.
(8) LANGE, B., AND LYDTIN, K.: Zeitschr. f. Tuberk., 1928, l, 45.
(9) GERLACH, F.: Ergebn. Hyg. Bakt. Immun. Forsch. u. exp. Therap., 1930, xi, 775.
(10) PRAUSNITZ, C.: Med. Welt., 1929, iii, 480.
(11) TZEKHNOVITZER, M.: Ann. l'Inst. Pasteur (supplement), 1928, xlii, 67.
(12) PARK, W. H.: Acta Paediat., 1931, xi, 395; Rev. Phtisiol. Méd. Soc., 1930, xi, 361.
(13) CANTACUZÈNE, J. *et al.*: Ann. l'Inst. Pasteur, 1927, xli, 274; 1928, xlii, 642; Arch. Roum. Path. Exper., 1929, ii, 131, & 1931, iv, 71.
(14) ALDERSHOFF, H.: Vaccination preventive de la tuberculose par le BCG. Rapports et documents, Inst. Pasteur, 1932, p. 187.
(15) GRIFFITH, A. S.: Lancet, 1932, i, 303.
(16) LANGE, B.: Ergebn d. gesamt. tuberkul. Forsch., 1930, i, 263.
(17) SAENZ, A.: Compt. Rend. Soc. Biol., 1931, cviii, 854; Lancet, 1931, ii, 1406.
(18) BOQUET, A.: Ann. l'Inst. Pasteur, 1931, xlvii, 117.
(19) LOEWENSTEIN, E.: Wien. klin. Wchnschr., 1926, xxxix, 293.
(20) GALLI-VALERIO, B.: Rev. Méd. Suisse Rom., 1927, xlvii, 169.
(21) ARMENGOL, R. P.: La Clinica, 1928 (November), p. 321.
(22) WATSON, E. A.: J. Am. Vet. Med. Assn., 1928, lxxiii, 799; XI Internat. Vet. Congress, London, 1930: General meeting, no. 2.
(23) CHIARI, H., NOBEL, E., AND SOLÉ, A.: Ztschr. f. Tuberk., 1928, l, 24, & li, 354.
(24) KORSCHUN, S. W., DWIJKOW, P. P., AND GOROCHOWNIKOWA, A. J.: Zentr. f. Bakt., Orig., I., 1929, cix, 297.
(25) SELTER, H., AND BLUMENBERG, W.: Klin. Wchnschr., 1927, vi (i), 1134 (June 11).

(26) SASANO, K. T., AND MEDLAR, E. M.: Amer. Rev. Tuberc., 1931, xxiii, 215; Tubercle, 1931, xii, 214.
(27) KRAUS, R.: Ztschr. f. Immunitaetsforsch. u. exp. Therap., 1927, li, 230; 1929, lxi, 454.
(28) KING, M. J., AND PARK, W. H.: Am. J. Publ. Health, 1929, xix, 179.
(29) GERLACH, F.: Ztschr. f. Immunitaetsforsch u. exp. Therap., 1927, li, 256; Ergebn. Hyg. Bakt. Immunitaetsforsch. u. exp. Therap., 1930, xi, 775.

TUBERCULOSIS AND LEUKAEMIA[1]

R. H. JAFFÉ

Since its first description by Virchow the combination of leukaemia and tuberculosis has attracted much interest, and the literature contains a considerable number of reports on the simultaneous occurrence of the two diseases (Boatini, Bruchmann, Dock, Eckel, Fuechtner, Hemmerling and Schleussing, Hirschfeld, Holler, Hyler, Jünger, Kast, Krasso and Nothnagel, Lichtheim, Lorenzetti, Margreth, Moenckeberg, Mueller and Grossmann, Nanta, Quincke, Roth, Schilling, Swirtschewskaya, Tiemann, Wiesenthal, and others). Though in some instances leukaemia and tuberculosis seemed to have existed together without markedly influencing their course, in the majority of the cases a certain antagonism could be noted in so far that either the tuberculosis changed the leukaemic picture or the leukaemia altered the anatomical manifestations of the tuberculous infection. Susmann discusses two possibilities, namely, that a latent tuberculosis may become activated under the influence of the leukaemia or that the leukaemia may so diminish the resistance of the body as to make it susceptible to a new infection. Some authors believe that the tuberculosis, under certain conditions, may cause the leukaemia (Hemmerling and Schleussing, Swirtschewskaja, Roth, Boatini, etc.), while others assume that the tuberculosis may produce only leukaemoid blood changes but not a true leukaemia.

Tiemann, who examined 75 cases of acute and chronic lymphatic and myelogenous leukaemia for the presence of an active tuberculosis, observed a generalized tuberculosis in but one instance of an acute lymphatic leukaemia. Among 30 cases of leukaemia I have seen three with active tuberculous lesions. These three cases form the material for my publication.

Cases

1: A white man, aged 46, received a crushing injury of his right thumb in December, 1928. While in the hospital he noticed for the first time that the lower half of his abdomen increased in size. This swelling of the abdomen

[1] From the Department of Pathology of the Cook County Hospital and Uihlein Memorial Laboratory, Grant Hospital, Chicago, Illinois.

gradually became more marked, involving also the upper half. During the last year the patient had several attacks of epistaxis, and a slight dyspnoea developed. He entered the hospital again in September, 1929. At the time of his admission his temperature was around 98°, his pulse-rate 90, his respiratory rate 22, and his blood-pressure 125/80. Over the bases of both lungs moist râles were heard. The abdomen was markedly distended, and over the chest and abdomen the superficial veins were dilated. The spleen extended to the iliac crest. The liver could not be palpated and there was no lymphadenopathy. There was a moderate oedema of the scrotum and of both lower extremities.

Blood Findings: Erythrocytes 800,000; haemoglobin 20 per cent; white blood cells 500,000: myeloblasts 2, promyelocytes 20, metamyelocytes 27, neutrophiles 40, lymphocytes 10, monocytes 1 per cent. Blood urea 8.46 mgm. Kahn reaction of blood two-plus positive.

Clinical Diagnosis: Chronic myelogenous leukaemia.

Soon after his admission the patient began to complain of numbness and pain in the right leg. A thrombosis of the femoral vein was diagnosed and the condition improved under light cradle and elevation. Roentgen radiation of the spleen was started, with the effect that the spleen decreased in size and that the white count dropped to 400,000. By the middle of December the patient's temperature began to rise every day to 100°F. interrupted by intervals of a week or two in which the temperature was normal. No further X-ray treatment was given. The blood picture now was quite different from the previous counts. The red blood cells amounted to 2,750,000, the haemoglobin was 60 per cent and the white count was 65,000: 30 per cent of the cells were neutrophilic myelocytes. Once the patient pulled out a loose tooth which was followed by a brisk haemorrhage.

In January, 1930, the patient felt quite well and spent most of the time out of bed. His right knee was somewhat stiff but this too gradually improved. His white count fluctuated between 30,000 and 40,000 without marked changes in the differential count. Early in March the temperature again went up to 99° and 100°F., and a roentgen examination of the chest disclosed diffuse infiltrations in both upper lung fields. Repeated examinations of the sputum failed, however, to show tubercle bacilli. A few weeks later a persistent diarrhoea developed. Blood findings, April 1, 1930, were erythrocytes 3,010,000, haemoglobin 65 per cent, white blood cells 25,750: myeloblasts 0.5, neutrophilic myelocytes 15.5, neutrophilic leucocytes 59, eosinophilic leucocytes 0.5, basophilic leucocytes 2.5, monocytes 9.5, lymphocytes 12.5 per cent. The patient went rapidly downhill and died April 17, 1930.

Abstract of Autopsy Findings: Length 64 inches; weight 77 pounds. The superficial lymph nodes were shot-like, discrete and firm. There were dense

fibrous adhesions about the lateral and posterior aspects of the right lung. The three lobes contained numerous nodules of firm consistency and of even size. The apex and the subapical portion of the upper lobe were indurated, and on section revealed a dense anthracotic scar-tissue surrounding dry cheesy and chalky nodules, from 2 to 4 mm. in diameter, which were arranged about the apical and subapical bronchi. The lumen of these bronchi was dilated and filled with mucopurulent material. The remaining portions of the lung were studded by peribronchial groups of light yellow-gray nodules. In the lower lobe there was also a larger, irregular area of diffuse caseation. The left lung showed a similar picture, except that in the lower lobe the nodules were scanty. The lymph nodes at the hilum of the lungs and at the bifurcation of the trachea measured up to 18 mm. in diameter, and were firm and deeply anthracotic.

Heart 225 gm.; spleen 400 gm., 18 by 8 by 6 cm. The consistence of the spleen was firm, and on the convex surface there was a whitish thickening of the capsule and several light yellow nodules, up to 3 mm. in diameter. The pulp was purple-red and the trabeculae were distinct. Near the lower pole there was an irregular, light yellow, homogeneous area. Liver 2250 gm.: its consistence was diminished and the surface was smooth and light gray-brown in color. On the sectioned surface were visible purplish-gray acinar markings and a few pinhead yellowish-gray nodules. In the lower jejunum, ileum and caecum were many transverse ulcers, up to 8 by 20 mm. in diameter, which had indurated, indented edges and a finely granular floor. The right adrenal contained a firm, yellow-gray node (2 by 1 by 4 cm.), which occupied the medulla. Kidneys 325 gm. In the intestine were blood-tinted tarry contents. The abdominal lymph nodes were up to 20 mm. in greatest diameter, and were soft and light yellow to yellow-gray. The bone-marrow was firm and light gray-brown.

Histological Findings: The bone-marrow was uniformly cellular. The following cell types were encountered: myeloblasts 11.2, neutrophilic myelocytes 14.2, neutrophilic leucocytes 29.2, oxyphilic myelocytes 1.0, oxyphilic leucocytes 0.2, erythrogonia 10.8, erythroblasts 11.6, normoblasts 16.8, megakaryocytes 0.2, megakaryoblasts 0.4, lymphocytes 1.2, and plasma cells 3.2 per cent. The pulp of the spleen contained a large number of neutrophilic myelocytes between which were scattered neutrophilic leucocytes, oxyphilic myelocytes and leucocytes, small groups of plasma cells, and single normoblasts. The follicles were reduced to small periarterial accumulations of lymphocytes. There was no thickening of the reticulum and the trabeculae appeared quite far apart. In the pulp a few small epithelioid-cell tubercles with giant cells were found. They did not differ from the usual picture and in the centre there was a zone of caseation. In the portal capillaries of the liver only a small number of nucleated cells was present. They could be identified as polymorphonuclear neutro-

philic leucocytes, myelocytes, and plasma cells. The Kupffer cells contained blood-pigment and a few erythrocytes. The liver cells of the central portions of the lobules were filled with large fat droplets, and the periportal tissue was loosely infiltrated by lymphocytes, plasma cells and mature leucocytes. In the periphery of the lobules, closely adjacent to and extending into the periportal tissue, single epithelioid-cell tubercles were present. They resembled those seen in the spleen. The peripancreatic, mesenteric and axillary lymph nodes contained many epithelioid-cell tubercles with central caseation and numerous giant cells. The intervening tissue consisted of small lymphocytes and occasional plasma cells. There was a hyalinic thickening of the reticulum which was most marked in the axillary lymph nodes. Stains for acid-fast bacilli revealed single slender and granular bacilli in the tubercles. The floor of the ulcers of the intestine was studded with epithelioid-cell tubercles, while the underlying submucosa was thickened and loosely infiltrated by lymphocytes, histiocytes and leucocytes. The majority of the nodules in the lungs were composed of a diffusely caseated centre, which followed the outlines of the bronchioli, extending in places into the adjacent alveoli. The caseated zone was surrounded by fibrillar connective tissue with focal round-cell accumulations, and there were only a very few giant cells and groups of epithelioid cells. The alveoli about the caseous areas were filled with a homogeneous, pale-stained material and large, vacuolated cells. In the caseous areas an enormous number of slender and segmented acid-fast bacilli could be demonstrated. The firm yellow-gray node in the right adrenal was composed of confluent areas of caseation, which were surrounded by epithelioid cells and occasional giant cells. The caseation extended into the periadrenal fat-tissue and in one place involved the wall of a larger branch of the suprarenal artery. A small number of acid-fast bacilli was found in the wall of the caseated artery. The microscopic examination of the kidneys and pancreas did not reveal any abnormal findings.

Anatomical Diagnosis: Acinous tuberculosis of both lungs and indurative tuberculosis of the apical and subapical portions of both upper pulmonary lobes. Caseous tuberculosis of the right adrenal. Tuberculous ulcers of the small intestine and caecum. Miliary tubercles in the liver and spleen. Myeloid metaplasia of the spleen. Active bone-marrow. Atrophy and parenchymatous degeneration of the myocardium. Cloudy swelling and slight fatty changes of the liver. Recent tuberculosis of the abdominal lymph nodes. Tar-colored intestinal contents. Haemorrhagic erosions of the stomach.

2: The interesting haematological findings of this case have been discussed in detail elsewhere.[2] They consisted of a slowly progressing anaemia, a persistent leucocytosis of between 32,000 and 78,000 cells and a predominance of

[2] R. H. Jaffé: The reticulo-endothelial system, Downey's *Pathology* (in press).

mature, young and immature monocytic elements which formed up to 57 per cent of the white blood cells. There were between 1 and 2 per cent myeloblasts and up to 21 per cent neutrophilic myelocytes. The patient was a white man, aged 67 years, who was under ambulatory observation for about a year. His chief complaints were stiffness of the joints and epigastric tenderness. Five years before his present illness he had his teeth extracted for alveolar pyorrhoea after which persistent ulcerations developed in the oral mucosa. They gradually cleared up under local treatment. During the year of observation the spleen became enlarged, until it extended two fingers below the costal arch. The superficial lymph nodes were slightly enlarged from the beginning. The patient was able to do his work as a superintendent of streetcars, but in the latter part of 1930 he was troubled by repeated "severe colds" from which he could not recover. He lost 20 pounds and entered the hospital in February, 1931, in a stage of extreme exhaustion. Three days after admission he died.

Abstract of Autopsy Findings: The abdominal cavity contained 1000 cc. of a turbid straw-colored fluid. The peritoneum was studded by numerous millet-seed-sized light gray nodules. Between the liver, the anterior abdominal wall and the diaphragm were veil-like adhesions which broke very easily. Each pleural cavity contained 2000 cc. of a clear straw-colored fluid, and the apices of both lungs were adherent to the thoracic wall. The pericardial sac was obliterated. In the apex of the left *lung* there was a subpleural, deeply anthracotic scar, which extended for 2 cm. into the lung. It surrounded the apical bronchus which was dilated. Below this scar, involving the upper third of the upper-lobe groups, pinhead-sized yellow-gray nodules were present. The other portions of the lungs were crepitant and moist, and in the basal part of the right lung a subpleural calcified nodule was found. The tracheobronchial lymph nodes contained many stony concretions. The heart was slightly hypertrophic, the cusps of the mitral valve were deformed by fibrotic nodules, and the myocardium was dark brown and friable. The spleen weighed 548 gm. It was firm and dark purple-gray, with fairly distinct trabeculae. The weight of the liver was 1660 gm. About the head of the pancreas was a group of enlarged lymph nodes, which contained chalky grayish-white concretions up to 15 mm. in diameter. The other organs did not reveal any unusual findings except for a marked anaemia. The bone-marrow was quite soft and light brown.

Histological Findings: In the bone-marrow was an enormous predominance of young neutrophilic myelocytes. There were very few other cell forms, namely, small groups of myeloblasts, eosinophilic leucocytes and normoblasts. The reticular cells were swollen and contained red blood cells and iron pigment. The pulp of the spleen was transformed into myeloid tissue which, similar to

the bone-marrow, showed a great many neutrophilic myelocytes. These cells were mixed with a few neutrophilic and oxyphilic leucocytes, lymphocytes, plasma cells and iron-filled histiocytes. In the liver the capillaries were filled with myelocytes, and there were small groups of myeloblasts and a few mature leucocytes. The Kupffer cells were very prominent and often formed small intraäcinar nodules. In addition to the proliferated stellate cells these nodules contained mature leucocytes and a few myelocytes. The periportal septa were infiltrated by myelocytes. The lymph nodes showed a swelling and proliferation of the reticular cells and in the medulla were groups of young neutrophilic myelocytes. The central portion of the peripancreatic lymph nodes was occupied by areas of diffuse caseation which were separated from the rest of the gland by a layer of fibrillar connective tissue. Outside this capsule there were small epithelioid-cell tubercles with giant cells and beginning central caseation. In the left upper pulmonary lobe were many areas of caseation surrounded by a wall of epithelioid-cell tubercles. Some of the caseated areas seemed to originate from bronchioli, the lumina of which were filled with necrotic material and cellular debris. Tubercle bacilli were present in small numbers. The nodules of the peritoneum were composed of epithelioid cells and giant cells, with a peripheral zone of small round cells. The centres of most of the nodules were caseated.

Anatomical Diagnosis: Indurative tuberculosis of the apex of the left lung with recent peribronchial spreading. Endoglandular tuberculous exacerbation in the peripancreatic lymph nodes. Recent tuberculous peritonitis. Extensive myeloid metaplasia of the spleen and liver and focal myeloid metaplasia of the lymph nodes. Active granulopoietic bone-marrow. Swelling and proliferation of the reticulo-histiocytes of the liver and lymph nodes. Fibrous obliteration of the pericardial sac and fibroplastic deformity of the mitral valve. Ascites and bilateral hydrothorax. Severe generalized anaemia.

3: The patient, a white male, 21 years of age, entered the hospital July 2, 1930. He complained of a hard mass in the abdomen which he had first observed two months before. Seven years earlier he had a swelling in the left submaxillary region, which was painless and remained stationary in size. At the age of seven the patient had had a tuberculosis of the left hip-joint which became ankylosed after treatment. At the time of his admission to the hospital the left submaxillary lymph nodes were moderately enlarged, firm and discrete. The spleen was so large that it occupied almost the entire left half of the abdominal cavity. The cervical, epitrochlear, axillary and inguinal lymph nodes were up to cherry size.

Blood Findings: White cells 366,000. No differential count was made at this time, but it was stated that the great majority of the cells were neutrophilic myelocytes and metamyelocytes. After radiation the spleen became smaller

and the number of the white cells decreased to 191,000. The patient felt so well that he went home. However, two months later, August 17, he returned, stating that for several days he had been bleeding from the nose and gums and that he felt very weak. He was now very anaemic and the superficial lymph nodes were larger than at the time of his first admission. Numerous purpuric spots were found over the arms and legs. The lower pole of the spleen was palpated four fingers below the costal arch.

Blood Findings: Erythrocytes 3,200,000; haemoglobin 50 per cent; white cells 208,000; myeloblasts 71, promyelocytes 3, neutrophilic metamyelocytes 4, neutrophilic leucocytes 17, eosinophilic myelocytes 1, eosinophilic leucocytes 1, basophilic leucocytes 2, lymphocytes 1 per cent. The myeloblasts were small, and only slightly larger than lymphocytes. The round nuclei showed a reticular chromatin structure, an indistinct membrane and one or two small nucleoli. The nuclei were surrounded by a narrow rim of basophilic cytoplasm which was homogeneous and did not give the oxydase reaction.

Under a rapidly progressing anaemia, the red count dropping to less than two millions within a few days, the patient expired one week after his second admission.

Abstract of Autopsy Findings: Length 73.5 inches; weight 122 pounds. Axillary lymph nodes walnut-sized; inguinal lymph nodes slightly larger; the left epitrochlear lymph node pea-sized. Purple-red patches over the abdomen, arms and legs. The left lower extremity is 7 cm. shorter than the right, the hip-joint is ankylosed and below the greater trochanter there is a 5 by 1.5 cm. scar.

Numerous deep red patches in the visceral and parietal peritoneum. The lungs distended and crepitant, with circumscribed fibrous adhesions about the base of both lower lobes. Small stony concretions in the lymph nodes at the hilum of both lungs and at the bifurcation of the trachea. Thymus replaced by fat-tissue. Heart weight 330 gm. The myocardium pale brown with purple-red patches in the epicardium. Spleen weight 2480 gm.; 33 by 21 by 10 cm.; firm and partially adherent to the anterior abdominal wall and diaphragm; the surface light purple and showing single slightly depressed, yellowish areas up to 2 cm. in diameter; on the sectioned surface the pulp light purple-red; the trabeculae visible as fine gray-white lines, and the depressed areas extending for 6 mm. into the pulp. Liver 2280 gm.; consistence soft; color light brown, with fine pale gray lines. Kidneys 340 gm.; the cortex containing several whitish areas, the largest 11 mm. in diameter, well separated from the light gray-brown parenchyma. The average size of the abdominal and retroperitoneal lymph nodes was 25 by 20 by 15 mm. The right submaxillary lymph nodes measured 30 mm. in greatest diameter and contained dry cheesy areas. The right adrenal weighed 10 gm.; the medulla was gray-white and about half

of the cortex was replaced by a dry, light yellow-gray node. The left adrenal was absent.

Histological Findings: The bone-marrow, which was very cellular, was made up chiefly of round cells which were about 8 micra in diameter. The nuclei of these cells were round or slightly indented and contained a fine, dust-like chromatin granulation, which was more marked near the membrane than in the centre. The nuclei were surrounded by a narrow rim of basophilic cytoplasm. Mitoses were numerous and showed short and thick chromosomes. Between these cells were single larger cells, the cytoplasm of which contained a very fine neutrophilic granulation. In some places the granulated cells formed small groups. There were also a few cells, with deeply stained lobulated nuclei and a similar granulation or with an oxyphilic granulation. Another type of cell was characterized by a homogeneous, oxychromatic cytoplasm and round dark nuclei. The reticular cells were swollen and contained engulfed red blood cells. The capillaries were dilated and filled by the cells found between them. The pulp of the spleen consisted chiefly of the round cells described in the bone-marrow. These cells did not give the oxydase reaction while there were single larger cells which were filled by oxydase granules. Oxyphilic granulocytes were more numerous than in the bone-marrow and there were also a few well-developed megakaryocytes which were not present in the marrow. The follicles were small, and composed of lymphocytes, the nuclear structure of which was distinctly different from that of the cells in the pulp. The portal capillaries of the liver were packed with nucleated elements and the round cells again outnumbered the other cell forms. There were small intracapillary groups of cells with a distinct oxydase granulation and single nucleated red blood cells. The Kupffer cells were much swollen, and stuffed with phagocytized round cells and erythrocytes. The periportal septa were infiltrated by lymphocytes, lymphoid round cells and the cells described in the capillary lumina. In the liver cells many iron granules could be demonstrated. The whitish areas in the cortex of the kidneys were found to be composed of the round cells described in the bone-marrow, spleen and liver. These cells were embedded in a delicate reticulum and separated the tubuli and glomeruli without invading them. The lymph nodes had retained their normal structure, except for small groups of oxydase-positive round cells in the medulla. Similar cells filled the dilated sinuses, which contained also mature neutrophilic and oxyphilic leucocytes. In the endothelial cells iron pigment could be demonstrated. A submaxillary lymph node contained an area of diffuse caseation, which was surrounded by a capsule of dense connective tissue. In many places the caseated material was impregnated by lime salts. Near the fibrotic capsule there were several groups of young epithelioid-cell tubercles with giant cells and central caseation. These tubercles contained single acid-fast bacilli. The middle third of the right adrenal was

the site of an irregular area of necrosis which affected mainly the cortex. In this necrotic area the outlines of the cortical cells were sometimes still discernible, and scattered throughout the necrosis were pyknotic, elongated, broken-up and segmented nuclei. Where the necrosis bordered on the capsule, the latter was thickened and loosely infiltrated with small round cells. The necrosis passed into the intact cortex without a sharp line of demarcation (figure 1).

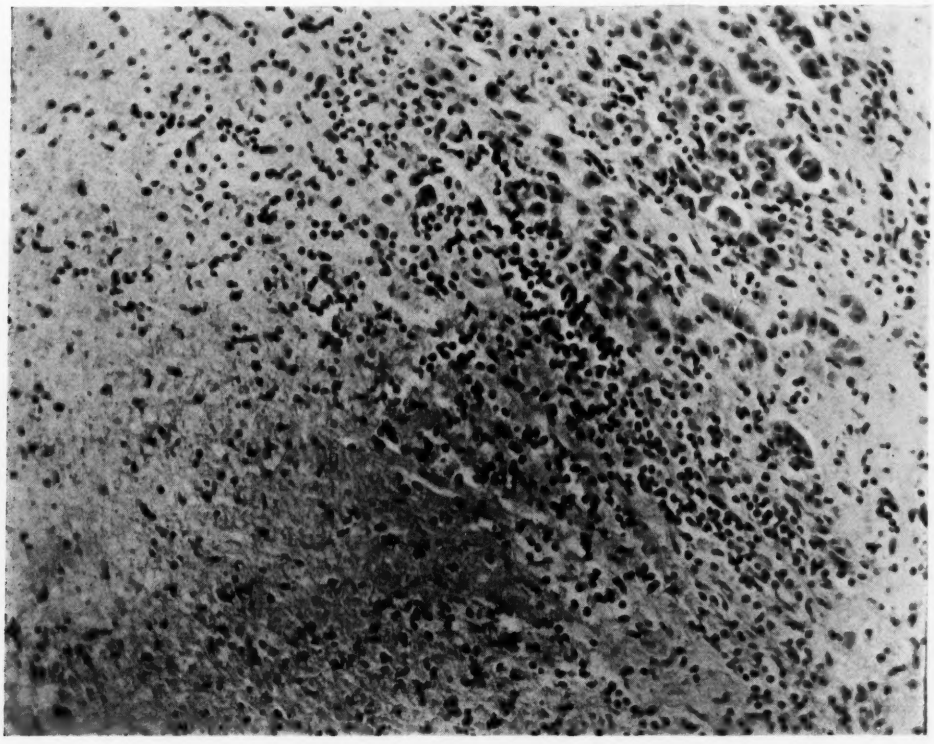


FIG. 1. Tuberculosis of the adrenal: case 3. Note the primary tissue necrosis without reactive changes. The capillaries near the necrosis are filled with micromyeloblasts which in the necrotic area break up and disappear. Magnification 300 times. Haemalum-eosin stain.

The cortical cells, which contained but little fat, lost their granular appearance and became homogeneous, and the nuclei disappeared. The capillaries were wide and filled with round mononuclear cells, and their endothelium was swollen. By passing into the necrotic area the nuclei of the endothelial cells assumed bizarre shapes. They were drawn out into long and beaded shreds or were twisted and segmented. The cells in the lumina of the capillaries were the round elements which dominated the histological picture of the blood-

forming organs. For a short distance inside the necrosis these cells remained well preserved, but passing beyond the marginal zone the cells became disintegrated. Epithelioid cells or giant cells were not found. There were very few small acid-fast round granules. The other organs do not require description of the microscopic findings.

Anatomical Diagnosis: Chronic myelogenous leukaemia with acute micromyeloblastic exacerbation. Petechial haemorrhages in the skin, epicardium, endocardium and peritoneum. Severe fatty degeneration of the myocardium. Marked anemia of the organs. Fibrocalcareous tuberculosis of the right submaxillary lymph nodes, with acute exacerbation. Caseous tuberculosis of the right adrenal. Aplasia of the left adrenal. Old ankylosis of the left hip-joint.

DISCUSSION

In discussing the influence which leukaemia and tuberculosis exert upon each other, one is met with the difficulty of distinguishing between true leukaemia and leukaemoid changes which may eventually result from the tuberculous infection. Since there is no sharp border-line between these leukaemoid changes and true leukaemia, the interpretation of some of the cases will remain in suspense. Leukaemoid blood pictures have been repeatedly described in tuberculosis. Thus, Marzullo and de Veer published two cases of tuberculosis with the clinical findings of an acute myelogenous leukaemia, which they attributed to the tuberculosis. One of the cases showed an indurative pulmonary tuberculosis with a marked anaemia and a leucocytosis which later turned into a leucopoenia. Of the leucocytes up to 72 per cent were oxydase-positive myeloblasts and up to 13 per cent neutrophilic myelocytes. The spleen weighed only 190 gm., and its pulp contained myelocytes and lymphocytes in about equal number. In the bone-marrow of the ribs a predominance of myeloblasts was found and there were many myelocytes in the mesenteric lymph nodes. The liver, however, was free from myeloid changes. The second case was one of tuberculous pneumonia. The blood picture was characterized by an anaemia, a transient leucocytosis and a very high percentage (up to 78 per cent) of immature granulocytes. In the pneumonic areas were observed an almost complete absence of productive changes and an enormous number of tubercle bacilli. The spleen was almost ten times normal size and contained many areas of caseation with a narrow epithelioid-cell margin. The pulp was rich in megakaryocytes and myeloblasts and there were a few myelocytes in the retroperitoneal and mesenteric lymph nodes. The bone-marrow of the ribs was fibrotic, with focal areas of lymphocytes, myeloblasts and myelocytes. The authors

considered the haematological changes of their cases as leukaemoid because characteristic leukaemic infiltrations were absent and the spleen and bone-marrow revealed but a moderate myeloid hyperplasia. The liver, in particular, did not contain myeloid tissue. A similar interpretation, namely, that of a "secondary myelosis" was given to a case of Gudzent by Lubarsch.

One has, however, to keep in mind that a tuberculosis which develops in a leukaemic organism often modifies the leukaemic process, and this occasionally so much so that during life or at autopsy the leukaemic changes are completely obscured (Holler, *et al.*). Hirschfeld states that the spontaneous remission of a leukaemia is frequently due to a complicating miliary tuberculosis. The intensity of the effect of the tuberculosis upon the leukaemia varies in the different cases; and there may be either a return of the blood findings to normal, or only a slight decrease of the white cells and a moderate to marked reduction of the extramedullary myelopoiesis, or no effect at all. The majority of the cases of leukaemia that die from tuberculosis do not show the typical anatomical picture of leukaemia.

Special attention has been given to the question of whether the tubercle bacillus, under certain conditions, may cause leukaemia. There can be little doubt that relations exist between infection and leukaemia, and especially the acute forms have often been interpreted as peculiar, though not specific reactions to infections (Sternberg, *et al.*). The primary factor, then, is an abnormal, constitutional irritability of the haemopoietic tissues which respond to a given infection with an excessive and atypical mobilization of the blood cells. Based upon their observations on a case of subacute leukaemic lymphadenosis, with a tuberculosis of the lymph nodes, solitary tubercle of the brain and tuberculous peritonitis, Hemmerling and Schleussing came to the conclusion that the tuberculous infection had acted as a nonspecific stimulant and had produced the leukaemia in a disposed individual. Roth, Eckel and Swirtschewskaja are of the same opinion, and believe that the leukaemia may be a response to the tuberculosis. Boatini, who stresses the existence of a true mixed lympho-myelogenous leukaemia, also assumes aetiological relations to exist between tuberculosis and leukaemia. In animals, too, leukaemia has been linked with tuberculosis. Burckhardt, for instance, sees in the myeloid leukaemia of fowls a manifestation of tuberculosis. Cash and Doan, however, have shown that the enormous leucocytosis found in pigeons with spontaneous tuberculosis is due only to an increase in number of

mature leucocytes, that in the bone-marrow myelocytes well advanced to maturity predominate, and that there is no extramedullary myelopoiesis.

In the first case of my series, the leukaemia undoubtedly preceded the fatal pulmonary tuberculosis. Though the clinical history mentioned previous attacks of epistaxis at the time of admission to the hospital no evidences of tuberculosis were found and the case was diagnosed as a frank chronic myelosis. It was during the stay in the hospital that an old and apparently latent apical pulmonary tuberculosis flared up, and I am inclined to link this flaring up with the intensive radiation of the spleen. Under the influence of the progressing pulmonary tuberculosis the leukaemia improved. Not only did the white count decrease considerably but also the red count rose and the patient felt quite well until an intestinal and terminal miliary tuberculosis developed. At autopsy the spleen, which once had extended to the iliac crest, weighed only 400 gm. The bone-marrow was hyperplastic, but the qualitative picture did not differ from that commonly seen in severe infections. The extramedullary blood-formation was restricted to the spleen. The histological manifestations of the tuberculous infection did not reveal any unusual features, and in the lymph nodes, liver and spleen typical epithelioid-cell tubercles and giant cells were found. The acinous lesions of the lung contained very many tubercle bacilli which were scanty in the other foci. The terminal miliary spread may have resulted from the invasion of a branch of the suprarenal artery. In this connection it may be mentioned that the combination of leukaemia and pulmonary tuberculosis is quite rare as compared with the extrapulmonary localization of the infection (Hirschfeld).

In the second case, which showed the persistent mononucleosis, the diagnosis of leukaemia may be questioned, since in grave cases of tuberculosis high monocyte counts are quite common. But the mononucleosis and the immature white blood cells were observed long before any signs of tuberculosis could be detected, and the atypical immature monocytic forms speak decidedly against a reactive monocytosis. In this case, too, I believe in the flaring up of a latent tuberculosis, the lowering of the resistance being due to the leukaemia. The anatomical findings support this explanation. There was a recent bronchial spreading from an indurated apical lesion in the left upper pulmonary lobe and there were also evidences of an activation in the peripancreatic lymph nodes which probably led to the tuberculous peritonitis. In this case the leukaemic changes were much more pronounced than in the first case and myeloid

tissue was found not only in the spleen but also in the liver and in the lymph nodes. The tuberculosis did not affect the leukaemia nor did the leukaemia influence the anatomical type of the tuberculosis. Moenckeberg believes that in the cases in which the leukaemia is not modified by the tuberculosis the latter shows a predominance of the primary necrosis over the productive changes. Siegmund speaks of an exhaustion of the active mesenchyma in leukaemia which causes an inability to produce tuberculous granulation tissue and an unchecked caseation. Krasso and Nothnagel described an atypical miliary tuberculosis in a case of chronic myelosis. The miliary tubercles were small anaemic infarcts, with such an enormous number of acid-fast bacilli that the authors assumed an infection with avian tubercle bacilli without, however, furnishing sufficient proof of their explanation. My first case showed a large number of tubercle bacilli in the lung lesions and very few bacilli in the other tuberculous areas, and yet there was no lack of cellular response. Simple tissue necrosis without proliferative reaction is not characteristic of tuberculosis in leukaemia and occurs in many instances in which the infection takes a rapid course.

Similar to the two other observations, case 3 illustrates the activation of a silent tuberculosis in leukaemia. The latent focus was found in a submaxillary lymph node, which contained an encapsulated fibrocaseous nodule surrounded by young epithelioid-cell tubercles. The activation led to a single distant metastasis in an hyperplastic adrenal, the hyperplasia being due to an aplasia of the other adrenal. The tuberculosis of the adrenal was early and formed merely an incidental finding, the patient dying from an acute micromyeloblastic exacerbation of the chronic myelosis. The lesion in the adrenal consisted of a primary tissue necrosis without epithelioid-cell reaction and, similar to Moenckeberg's case, only a few acid-fast granules could be detected in the necrotic area.

In none of my 3 cases were there any evidences for the leukaemic cells, in particular the myeloblasts, taking part in the defense against the infection. In case 3 the myeloblasts in the area of necrosis underwent the same regressive changes as the other cells without showing signs of a transformation into other cell forms. I am stressing this fact because Timofejewsky and Benewolenskaja described a great resistance of the leukaemic myeloblast to tubercle bacilli in tissue cultures. These authors infected explanted leukaemic blood with human tubercle bacilli and found that the myeloblasts phagocytized and destroyed the bacilli, and became transformed into epithelioid cells and giant cells of Langhans type.

In a preceding publication I have pointed out that the mesenchyme of the leukaemic organism is able to produce blood cells when it is irritated. The tubercle bacillus apparently suppresses the abnormal myelopoietic potencies of the leukaemic mesenchyme, and the response to the infection is not different from that seen in other individuals.

SUMMARY

Three cases of myelogenous leukaemia are described in which the autopsy disclosed the activation of an old and apparently silent tuberculosis. The first case died from an acinous-nodose pulmonary tuberculosis which had markedly influenced the leukaemia, improving the anaemia and decreasing the number of the white cells in the peripheral blood. Extramedullary myelopoiesis was found restricted to the spleen. In the second case a tuberculous peritonitis developed from the endoglandular exacerbation of tuberculous lesions in the peripancreatic lymph nodes. The tuberculosis had no effect upon the leukaemia. In these two instances the histological picture of the tuberculous changes did not reveal any peculiarities, and typical epithelioid cell tubercles with giant cells were found. The third case showed a recent caseating tuberculosis of the right adrenal, which was an incidental finding and was apparently secondary to the flaring up of an old focus in the right submaxillary lymph nodes. The process in the adrenal was characterized by the predominance of the primary tissue necrosis and the lack of cellular response. There were no evidences that the leukaemic cells took part in the defense reactions against the infection.

The relations between leukaemoid pictures and true leukaemia in tuberculosis are discussed.

BIBLIOGRAPHY

BOATINI, G.: Haematologica, 1931, xii, 423.
CASH, J. R., AND DOAN, C. A.: Am. J. Path., 1931, vii, 373.
DOCK, G.: Am. J. M. Sc., 1904, cxxvii, 563.
ECKEL, P.: Med. Klin., 1929, xxv, 223.
GUDZENT: Deutsch. med. Wchnschr., 1922, xlviii, 405.
HEMMERLING, H., AND SCHLEUSSING, H.: Deutsch. Arch. f. klin. Med., 1927, clvii, 309.
HIRSCHFELD, H.: Fol. Haematol., 1920, xxvi, 108; Handbuch der Krankheiten des Blutes und der blutbildenden Organe, J. Springer, Berlin, 1925, i, 334.
HOLLER, G.: Klin. Wchnschr., 1931, x, 1663.
JAFFÉ, R. H.: Arch. Path., 1932, xiv, 177.
JÜNGER: Virchow's Arch., 1900, clxii, 283.
KRASSO, H., AND NOTHNAGEL, H.: Wien. Arch. klin. Med., 1925, xi, 507.
LICHTHEIM: Deutsch. med. Wchnschr., 1897, xxiii, 183.

LORENZETTI: L'Ospedale Maggiore, 1925, xiii, 4.
LUBARSCH, O.: Deutsch. med. Wchnschr., 1922, xlviii, 787.
MARGRETH: Minerva Med., 1929, ix, 1.
MARZULLO, J. G., AND DE VEER, J. A.: Am. J. M. Sc., 1931, clxxxii, 372.
MÖNCKEBERG, J. G.: Verhandl. Deutsch. path. Ges., 1912, xii, 42.
NANTA, A.: Arch. de. Mal. du Coeur, 1913, vi, 37.
QUINCKE, H.: Deutsch. Arch. f. klin. Med., 1902, lxxiv, 445.
ROTH: Ztschr. f. klin. Med., 1913, lxxviii, 75.
SIEGMUND: Verhandl. Deutsch. path. Ges., 1923, xix, 114.
SWIRTSCHEWSKAJA, B.: Virchow's Arch., 1926, cclxii, 1.
TIEMANN: Klin. Wchnschr., 1930, ix, 1003.
TIMOFEJEWSKY, A. D., AND BENEWOLENSKAJA, S. H.: Virchow's Arch., 1927, cclxiv, 605.
SUSMANN: Practioner, 1903, part ii, 536.

BENIGN PULMONARY TUBERCULOSIS WITH DIABETES[1]

H. WESSLER AND HERMAN HENNELL

Ever since the association of tuberculosis and diabetes has been noted by clinicians, it has been generally believed that tuberculosis is a frequent complication of diabetes and that the latter disease exerts so unfavorable an influence on the tuberculosis that it acquires a progressive and usually fatal character.

The statistical studies of Montgomery (1), Fitz (2), and Joslin (3), however, do not confirm a greater incidence of tuberculosis in the diabetic, and one gains the impression from the recent literature that the susceptibility to tuberculosis is no greater in the diabetic than in the general population. A belief in the progressive character of the tuberculosis in diabetics, however, still persists although no satisfactory reasons have been advanced why this should be so. If the susceptibility to tuberculosis is not increased because of the presence of diabetes, it is not easy to understand why the former disease should take the progressive and fatal course which is commonly ascribed to it.

These considerations find support in our experience with tuberculosis in the diabetic during the past few years. We have observed a number of cases of tuberculosis whose benign character and tendency to cure lead us to believe that the traditional view in regard to the tuberculous infection in diabetes should be modified and that a more hopeful prognosis is justified.

A brief abstract of our cases follows:

Case 1: L. L. Male; age 44; first seen June 9, 1929, with a two months' history of cough, fever and pain in the chest; on two occasions the sputum was blood-tinged. *Examination:* Temperature 102.4°; moderate cough and expectoration; no tubercle bacilli. *Lungs:* Dulness and numerous crepitant râles in left upper lobe. *Urine:* 1 per cent sugar; blood sugar 230 mgm. *Roentgenogram* (figure 1): Showed dense circular infiltration in left lung from fifth to ninth rib posteriorly, with cavity 1.5 inches in diameter. Bronchoscopic examination negative.

Patient stayed in hospital seven weeks. Condition improved rapidly.

[1] From the Division of Thoracic Diseases, Mount Sinai Hospital, New York City.

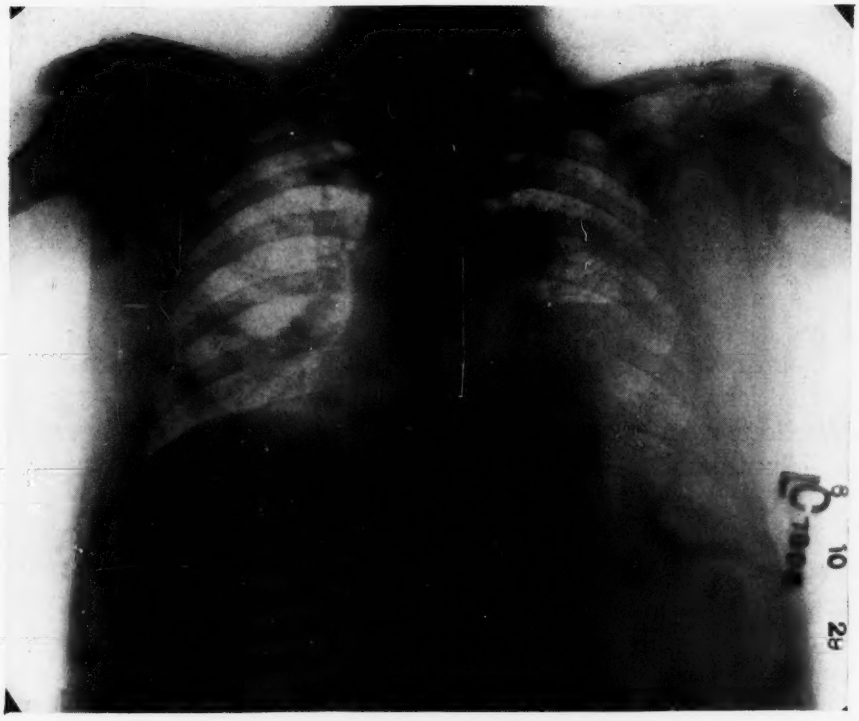


FIG. 1. Case 1. Exudative tuberculosis with large cavity in left lung

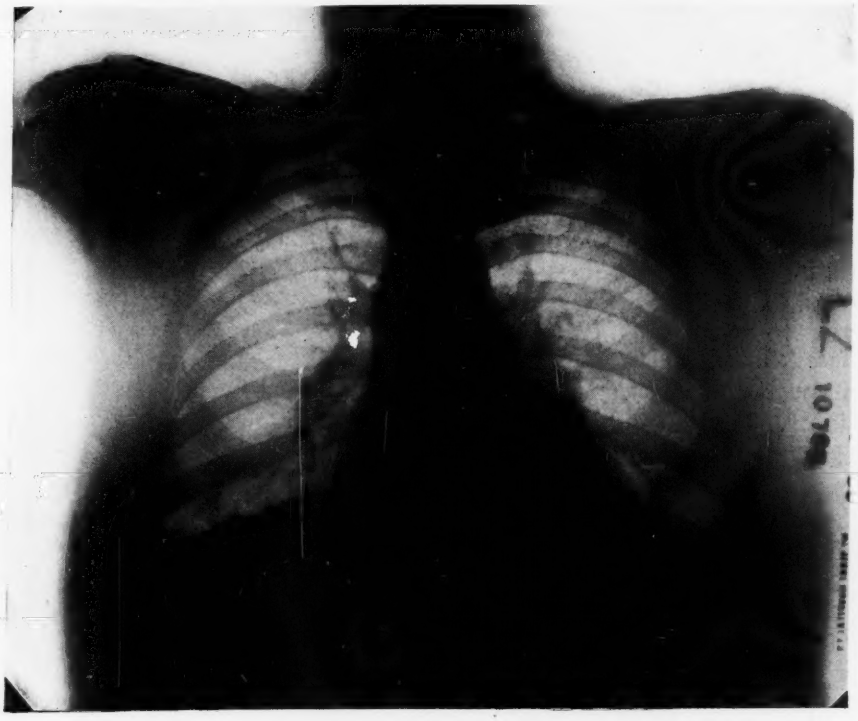


FIG. 2. Case 1. Complete cure in 2½ months with disappearance of cavity

Temperature became normal on the second day; cough and expectoration disappeared by end of fifth week. On discharge, patient was quite well and weight increased from 162 to 167 pounds. From that time until August, 1930, there was progressive absorption of infiltration in lungs, so that finally the cavity had disappeared and a small area of fibrosis remained at the site of his lesion (figure 2).

Comment: A case of exudative tuberculosis, with cavitation in a mild diabetic, which progressed to complete cure in a relatively short time.

Case 2: M. W. Female; age 60; severe diabetes for six years; at previous admission to hospital in September, 1929, for treatment of diabetes had no pulmonary disease. Present study began January 3, 1931, because of loss of 20 pounds, pain in right chest, night-sweats and dry cough for three months. Diabetes aggravated. *Examination:* Underweight, normal temperature, dry cough. *Lungs:* Moderate dulness, slightly altered breathing and inconstant râles over right upper lobe. *Urine:* Contained 6 per cent sugar and blood sugar was 310 mgm. *Roentgenogram:* Showed an exudative process in right upper lobe.

Patient remained in hospital seven weeks. Diabetes controlled by diet without insulin, and pulmonary symptoms disappeared. There was only a slight absorption of the tuberculous process. Patient observed finally on October 20, when she had gained considerable weight. Roentgenogram showed progressive fibrosis of right upper lobe. Patient had no symptoms.

Comment: A case of fairly extensive exudative tuberculosis in a diabetic of many years' standing in whom the process is undergoing fibrosis.

Case 3: D. E. Male; age 55; May, 1930. History of mild diabetes for eleven years; chronic cough; at this time cough and expectoration were insignificant. *Examination:* Mild diabetes. Signs and symptoms of spondylitis. No pulmonary physical signs. *Roentgen Examination:* Showed infiltration, with small cavity in left lower lobe (figure 3). Bronchoscopic examination negative.

Patient at hospital for five weeks, with improvement in condition. Diabetes controlled with diet and small amount of insulin. Pulmonary symptoms were minor. Tubercle bacilli not found. Patient under observation for one and a half years thereafter, during which tubercle bacilli were found in sputum on one occasion. Frequent roentgen examinations showed progressive absorption of infiltration and fibrosis and eventual disappearance of the cavity (figure 4).

Comment: A tuberculous process with cavity discovered only on roentgen examination in an elderly mild diabetic of many years' duration which underwent gradual fibrosis, with the disappearance of the cavity.

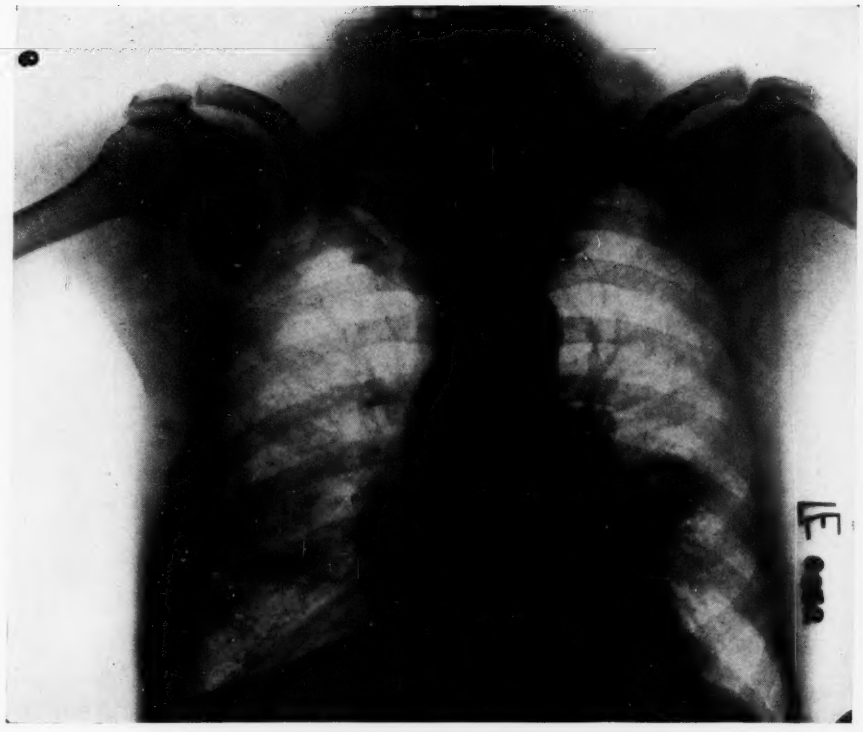


FIG. 3. Case 3. Infiltration with cavity in left lower lobe

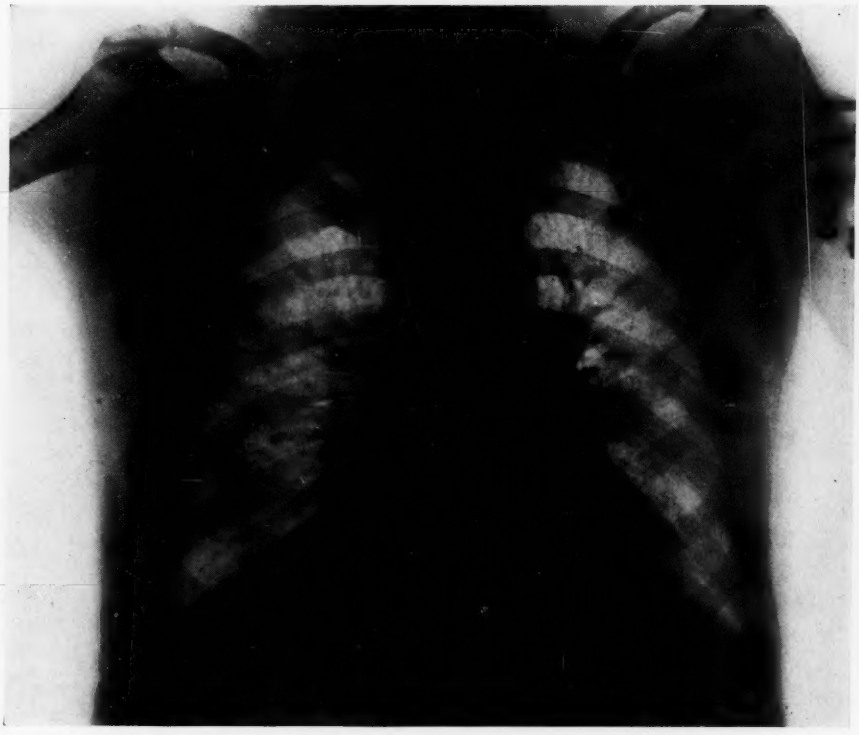


FIG. 4. Case 3. Almost complete absorption and disappearance of cavity, 1½ years later

FIG. 5. Case 5. Extensive exudative tuberculosis, right upper lobe, with a number of small cavities.

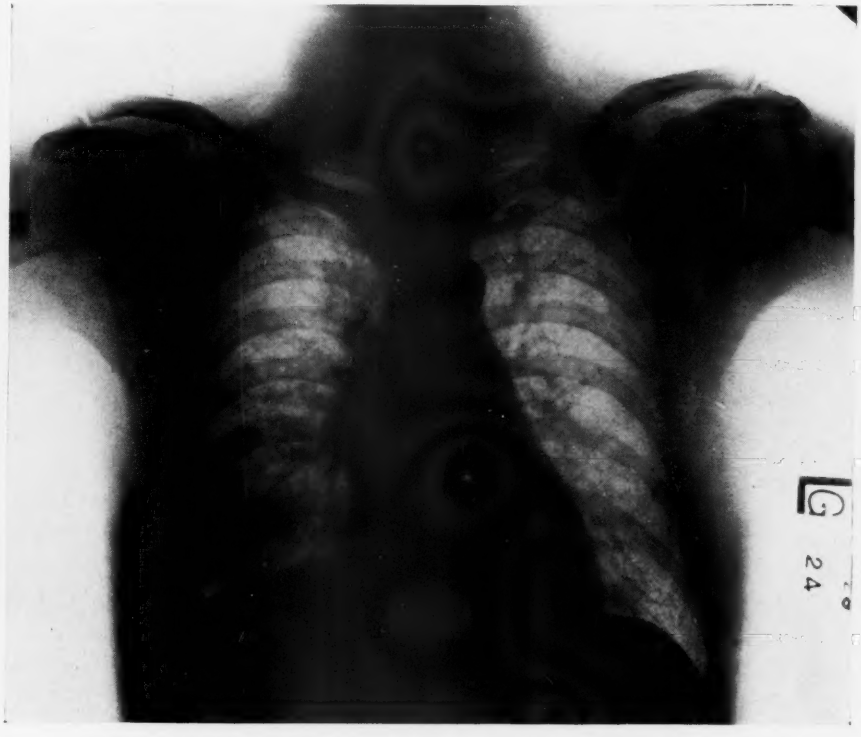


FIG. 6. Case 5. Absorption of infiltration in three months

Case 4: R. B. Female; age 31; October, 1931. Diabetes for six years and under dietetic control until two years before. During this time exposed to case of open tuberculosis. For three months cough, weakness and loss of 20 pounds. *Examination:* Poor nutrition; normal temperature; moderate dry cough. *Lungs:* Slight dulness and occasional râles left upper lobe. *Urine:* 3 per cent sugar, with trace of acetone; blood sugar 340 mgm. *Roentgenogram:* Showed infiltration in left upper lobe, exudative in type, enclosing cavity 1.5 inches in diameter; small exudative focus in lower part of right upper lobe.

Diabetes controlled by diet and 50 units of insulin. Pulmonary condition steadily improved, with beginning absorption. Two months after admission, however, because of persistence of cavitation, pneumothorax was induced; patient discharged January, 1932. Had gained 17 pounds and diabetes was under control. Patient continued treatment at sanatorium.

Comment: A case of exudative tuberculosis, with cavitation in a diabetic of long standing. The tuberculosis responded favorably to treatment, including pneumothorax. There is every reason to believe that this patient will go on to cure.

Case 5: H. S. Male; age 29; October, 1929. Symptoms of diabetes for three months, with loss of 20 pounds. No pulmonary symptoms. *Examination:* Showed moderately severe diabetes. *Lungs:* Impaired resonance and altered breathing in right lung, especially behind; no fever. *Roentgen Examination* (figure 5): Showed extensive exudative process of right lung, with a number of small cavities.

During three months in hospital, with diet and insulin, diabetes was controlled. Patient became free of symptoms and gained 27 pounds in weight. At no time did he have pulmonary symptoms, and physical signs remained insignificant. Successive roentgen examinations showed absorption of exudate of lung, and on discharge only a few fibrotic strands remained (figure 6).

Comment: An extensive, exudative process involving the right lung; it was more or less latent in a diabetic of moderate severity. The process healed completely in three months.

Case 6: M. L. Female; age 51; October, 1929. Diabetes first discovered in December, 1928. Present illness began three days before with fever and pain in right chest. *Examination:* Patient not acutely ill. Signs of infiltration in right upper lobe. *Roentgen Examination:* Showed infraclavicular infiltration on right side enclosing cavity (figure 7). Blood sugar 281 mgm. Symptoms improved rapidly and in two months infiltration had almost disappeared (figure 8).

Remained well until February, 1932, when readmitted to hospital. Had

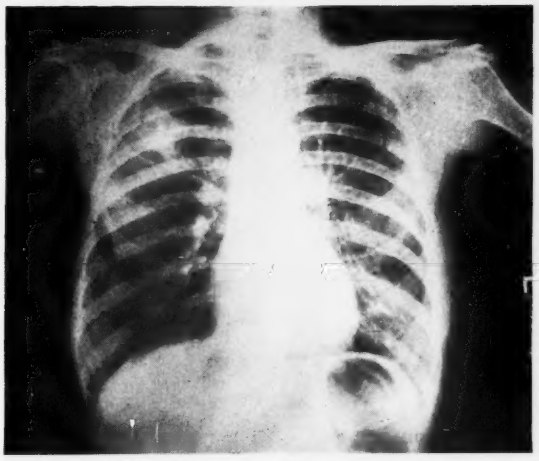


FIG. 7. Case 6. Tuberculosis of right infraclavicular region with cavity

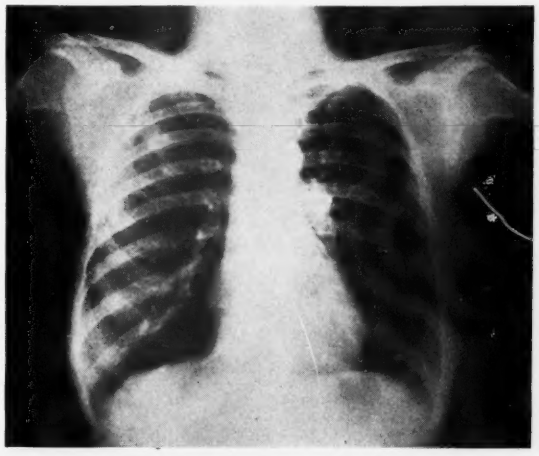


FIG. 8. Case 6. Two months later. Marked decrease in size of infiltration

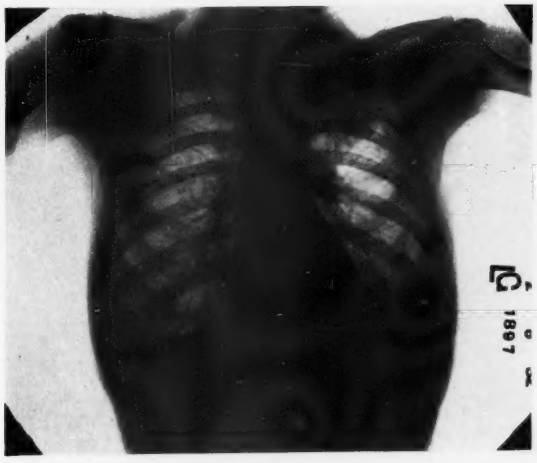


FIG. 9. Case 6. Two years later. Complete cure of process on right side with a fresh pneumonic process in left upper lobe. Latter is undergoing absorption.

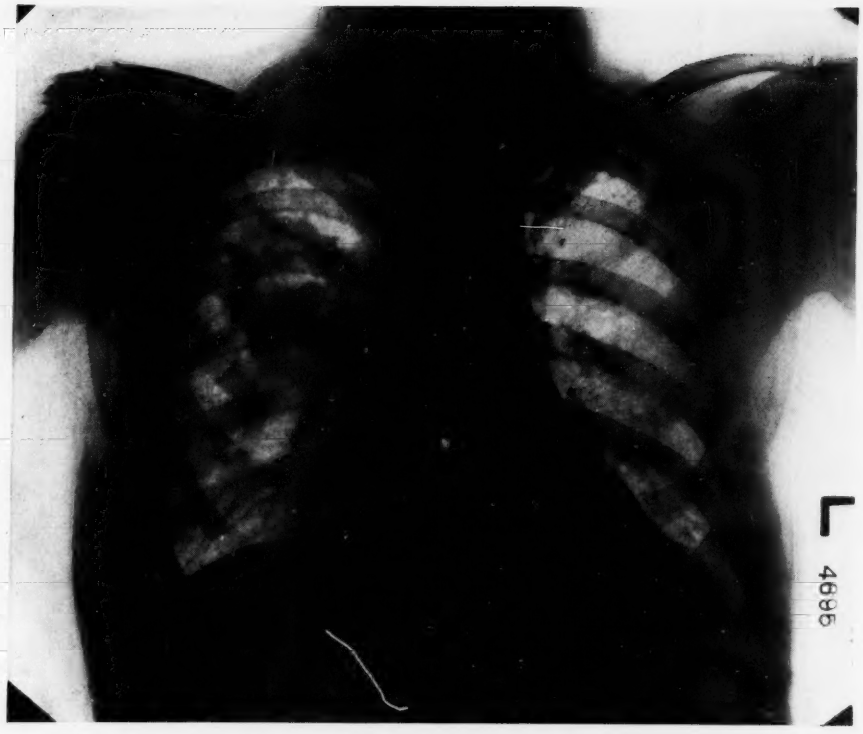


FIG. 10. Case 7. Extensive pneumonic tuberculosis of right upper lobe with large cavity

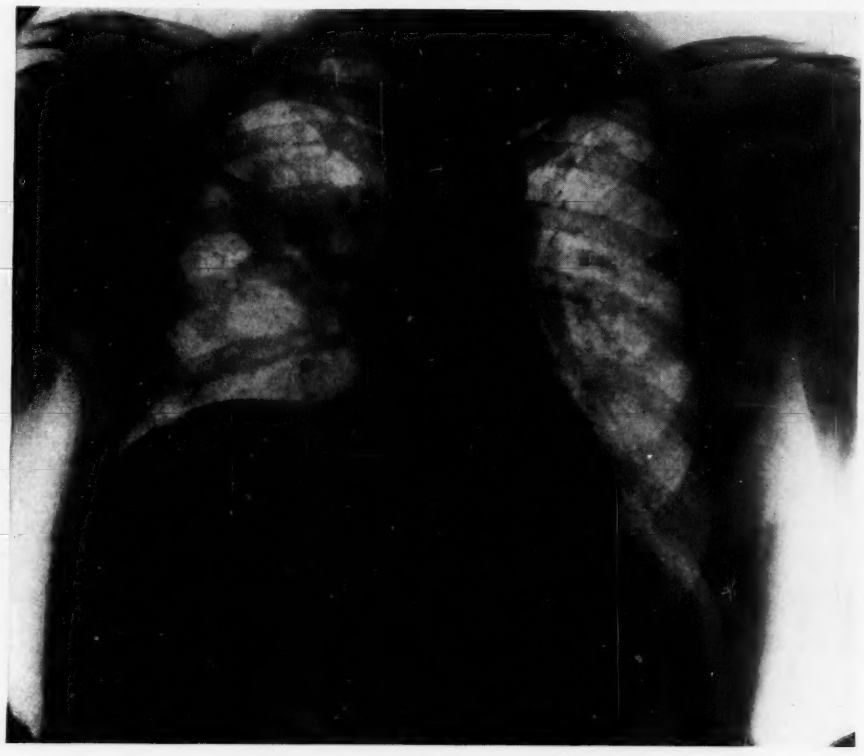


FIG. 11. Case 7. Marked absorption of infiltration and closure of cavity 5½ months later. Phrenicotomy.

then had a cold with fever and cough and blood-tinged sputum for one week. *Examination:* Temperature 102°; vague signs at the left apex. *Roentgen Examination* (figure 9): Showed pneumonic area at left apex. Patient had neglected her diet and blood sugar was 420 mgm. Was not acutely ill and symptoms promptly subsided. Infiltration gradually decreased in extent and, on discharge several weeks later, was well on the way to absorption.

Comment: A case of severe diabetes in which patient on two occasions had exudative tuberculosis, once with a cavity, which subsided under rest and appropriate dietetic treatment.

Case 7: J. J. C. Male; age 55; October 29, 1930. Had diabetes for one year, easily controlled by diet; after period of dietary neglect, three months ago began to cough with increasing expectoration; lost much weight; daily sweats. *Examination:* Poorly nourished man. Blood sugar 265 mgm. Physical signs of extensive infiltration in right upper lobe. *Roentgen Examination:* Showed an extensive exudative process in right upper lobe, with large cavity (figure 10). Sputum positive for tubercle bacilli. After period of observation and failure to induce pneumothorax, phrenicotomy performed.

Under dietetic treatment and insulin, made rapid improvement. Cough disappeared; rapid gain in weight. *Roentgen Examination* (figure 11): April 18, 1931: Showed marked elevation of right diaphragm, with considerable absorption of infiltration and beginning fibrosis. Cavity barely visible. Since then, patient has remained in good health without pulmonary symptoms.

Comment: An extensive exudative tuberculosis of recent development, with a large cavity which promptly retrogressed under diabetic treatment and phrenicotomy. The infiltrations are still present but are undergoing fibrosis.

Case 8: M. U. Male; age 55; May, 1931. Diabetes of several years' duration; for a few months loss of weight and slight dry cough. *Examination:* Well-nourished man. Moderate glycosuria. *Lungs:* Slight dulness, right upper lobe, with occasional râles. Sputum positive for tubercle bacilli. *Roentgenogram:* Pneumonic infiltration in right upper lobe enclosing small cavity (figure 12).

Patient placed on strict diabetic diet and rest. Cough promptly disappeared, and within six weeks cavity had disappeared. By September, 1931, there were no longer any physical signs and lungs had practically cleared up. Patient has stayed well to date and roentgen examination shows lungs to be clear (figure 13).

Comment: A case of tuberculosis in chronic diabetic. The process was in the acute exudative stage, with cavitation, which promptly cured on diabetic treatment and rest. There were minor constitutional symptoms.

FIG. 12. Case 8. Pneumonic tuberculosis of right upper lobe

FIG. 13. Case 8. Absorption of infiltration in 3½ months

In addition to the cases just summarized we have records of 3 patients which we do not report in detail because they are essentially similar. They are of interest because they showed, during the course of their diabetes, fugitive pneumonic infiltrations in the lungs, with minor pulmonary symptoms which rapidly retrogressed. Although tubercle bacilli were not found in the sputum of the patients, it is fair to exclude ordinary pneumonia as the cause of these infiltrations because they presented none of the symptoms or physical signs which would ordinarily be associated with pneumonia.

COMMENT

These cases are remarkable for the benign course which the tuberculosis pursued. The infection in most cases was of recent development. There was a minimum of fever which rapidly subsided, together with any cough or expectoration. Although the pulmonary lesion was always exudative in nature and was associated in a number of cases with cavity-formation, in none of the patients did it manifest a progressive tendency. On the contrary, with proper dietetic care under ordinary hospital conditions, the pulmonary infiltrations rapidly absorbed and in most of the cases went on to complete cure in a relatively short time. It is noteworthy that one patient (case 6) had two such episodes of tuberculous infection with cavity-formation at an interval of three years, both of which were successfully overcome.

When we investigate more closely the nature of the tuberculous process which was found in these patients, it is at once evident that it exhibited the usual character of this disease as it is found in the general population. As is well known, adult reinfection in tuberculosis is essentially an exudative process which begins usually in the subapical region of the lungs. This form of tuberculosis produces a minimum of physical signs and we owe our knowledge of it mainly to roentgen studies. It is often a benign infection and has a great tendency to undergo fairly rapid absorption. There is no doubt that many persons pass through such an infection under the guise of a "grippe" and that the tuberculous nature of the disease is unrecognized.

This must frequently have happened before the widespread use of the roentgen ray in the diagnosis of pulmonary tuberculosis. It is probable that diabetic patients also were affected by this form of tuberculosis and that many of them, like those here reported, overcame the infection. In the diabetic, especially in the absence of definite physical signs of pulmonary disease, such a tuberculosis would more easily be overlooked because the constitutional symptoms of this disease would find a plausible

explanation in the associated diabetes. In other cases, either because of the severity of the infection or the gravity of the diabetes, the tuberculosis would become manifest later when it had already reached an advanced stage. These were the cases which were probably aggravated by an uncontrollable diabetes and continued to a fatal termination. In this manner arose the belief in the virulent character of the tuberculosis which is current to this day.

The favorable outcome of our cases cannot be attributed to a mildness of the diabetes. Most of the patients had this disease for a number of years and showed a low sugar tolerance which could only be raised by the use of insulin. We therefore feel justified in the belief that the tuberculous infection in these patients did not differ fundamentally from that in the nondiabetic. It must furthermore be concluded that tuberculosis in the diabetic is not inherently or necessarily progressive or fatal. On the contrary, it may be a benign and curable infection.

It is not contended that the coexistence of the diabetes is a matter of indifference to the progress of the tuberculosis. However, the experiences here recorded afford grounds for the belief that, with modern methods for the control of diabetes, the benign forms of tuberculosis which we have shown to occur in diabetes may be readily checked in their inception before they have become advanced and incurable.

REFERENCES

(1) MONTGOMERY, C. M.: Am. J. M. Sc., 1912, cxliv, 547.
(2) FITZ, R.: Ibid., 1930, clxxx, 195.
(3) JOSLIN, E. P.: The treatment of diabetes mellitus, ed. 3, Lea & Febiger, p. 569.

CONGENITAL CYSTIC DISEASE OF THE LUNG[1]

WILLIAM C. POLLOCK[2] AND HORACE P. MARVIN[3]

Congenital cystic disease of the lung we believe to be a definite disease entity and one of extremely rare occurrence. The cystic condition of the lung is secondary to a narrowing of the main bronchus or bronchi of the involved lobe or lobes and it is this narrowing which is congenital.

The cystic changes, which develop as a result of bronchial restriction, are usually more or less stationary, but may be progressive under certain conditions. Usually there is only a congenital defect of the bronchus to one lobe and this more frequently of the upper lobe. In these cases there may be extensive cystic changes of the entire lobe without symptoms. When more than one lobe is involved, conditions of pulmonary stress by hyperphysical activity may cause a progression of the cystic disease, until symptoms of dyspnoea, cough, etc., develop.

The disease has been known to be present over a period of many years without symptoms. Cases have been discovered in early childhood by routine X-ray and followed for a period of ten years without pulmonary change or symptoms. Cystic disease is usually discovered accidentally by routine X-ray and not because of any symptoms referable to the chest. This disease entity is not to be confused with congenital bronchiectasis as there are no dilatations of the bronchi of the cystic lung.

In April 1927, Wilson (1) reported a case of "obstructive emphysema." We have a case under observation which we believe presents pulmonary pathological changes identical to those of Wilson's report. We have access to the clinical record of his case together with X-rays, and will refer to his case as well as give a photograph of the X-ray film. The two cases are similar in practically every detail except that Wilson's case presented the marked subjective and objective symptom of dyspnoea. This symptom was present to the degree of producing invalidism. Our case is as yet in a state of excellent health.

[1] Published with permission of the Surgeon General, U. S. Army, who is not responsible for any opinion expressed or conclusion reached herein.

[2] Major, U. S. Army, Medical Corps.

[3] Captain, U. S. Army, Medical Corps.

As pointed out by Wilson, "obstructive emphysema is mentioned in the literature almost without exception in connection with foreign bodies or tumors of the bronchial tubes." In the American literature we are unable to find reports of cases such as ours, in which the cystic changes are obstructive in character because of a narrowing of the main bronchus. We believe this to be the aetiological factor in both cases and that this factor is congenital, the emphysematous or cystic changes of the lung parenchyma being of a stationary or of a slowly progressive character.

Case Report

L. B. C. Adult, white, male, age 40 years. *Occupation:* Musician (drummer); played trombone in 1912. *Personal Habits:* Occasional drink; smokes package of cigarettes a day. *Family History:* Father 68 years, alive and well; mother 68 years, alive and well; one brother alive and well. *Previous Personal History:* Typhoid fever with double pneumonia at 5 years; malaria at 10 years; appendicectomy at 14 years; influenza, 1915, with two light attacks since that time. States that he has felt somewhat more tired with slight but noticeable shortness of breath during past 10 years. Has also been aware of slight cough, worse at intervals during past 8 years. In 1915 noticed severe palpitation for two consecutive nights which caused him to sit up in bed to "catch his breath."

Present Illness: Except for the above-noted facts, patient had been in good general health until June 15, 1931, at which time he was taking course in commercial school in Des Moines, Iowa. Condition began with chills and fever, which was 104°F. the first evening. Taken to hospital in Des Moines, where he remained under treatment for ten days. At that time patient reports that he had fluctuating temperature which gradually returned to normal. No increase in cough or expectoration. X-ray of chest was taken in hospital, and patient informed that he had pulmonary tuberculosis and that left upper lobe was collapsed down to 3rd rib in front and 7th rib posteriorly. Recovery of acute condition was uneventful, following which patient applied to Veterans Bureau for admission to a tuberculosis hospital.

Condition on Admission: Patient admitted to Fitzsimons General Hospital on July 6, 1931, for treatment of "advanced, active pulmonary tuberculosis." Complaints were general malaise, slight unproductive cough, and mild dyspnoea aggravated by exertion. Was afebrile, and without chest pains, night-sweats, haemoptysis, hoarseness or gastrointestinal symptoms of any kind. Appetite good, bowels regular, occasional nocturia, but no other genitourinary symptoms.

Physical Findings: A rather neurotic-appearing patient, weight 122 lbs., being 8 lbs. under normal. Palpebral fissure appeared slightly wider than normal, with eyeballs somewhat prominent. Skin normal. Thyroid pal-

pable, but not definitely enlarged. Vascular system normal. Blood-pressure 130/80. Pulse 92, regular. Heart-sounds normal in every way except for increased rate. *P. M. I.* in 5th interspace, 7.5 cm. to left midsternal line.

Chest Examination: Slight diminution in resonance, with increased voice-sounds at right apex. *Left lung:* Hyperresonant, very feeble breathing, and decreased vocal resonance and vocal fremitus. No râles. Coin-sound plus. Fine tremor of lids, tongue and extended fingers. Otherwise physical examination entirely normal.

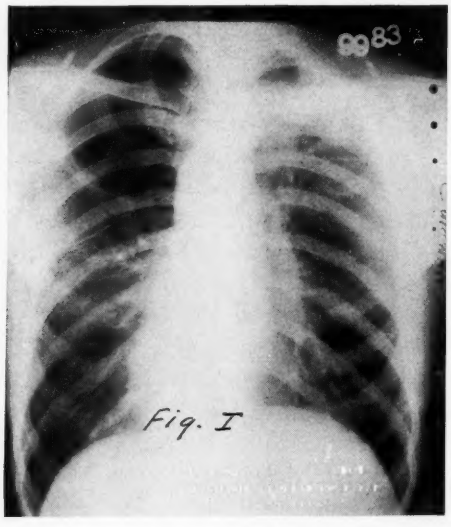
Laboratory Findings: Electrocardiogram normal. Seven urines all normal. Faeces normal. Eleven sputa negative for tubercle bacilli. Blood count: R. B. C. 5,100,000; W. B. C. 7,600; haemoglobin 80 per cent; small mononuclears 32, eosinophiles 4, neutrophiles 64; Wassermann and Kahn negative. B. M. R.: Sanborn minus 5; Haldane minus 4. Blood chemistry: Sugar 100; N. P. N. 30. No evidence of focal infection in throat or sinuses. Prostate negative. Vision and hearing normal.

Roentgen Report: Heart-shadow moderately distorted. Right leaf of diaphragm slightly irregular. Pleurae seem thickened bilaterally. Left upper lobe space distinctly larger than on right, with slight widening of the intercostal spaces. No displacement of the mediastinum or of mediastinal organs. *Right lung:* Shows fine but moderately heavy seeding of discrete nodose involvement in upper portion of upper lobe, the greatest involvement being in the first intercostal space where lesions tend to be conglomerate. There is no perifocal reaction and the process seems to be arrested or quiescent. *Left lung:* Above second rib is total absence of lung structure. No definite structure made out until level of 3rd rib anteriorly. In this area is a distinct dense fine line traversing the space in a downward-upward sweeping curve. The line extends well out to the periphery and marks lower border of the apparent structureless area above. Another similar line is seen at level of 4th rib. This line extends downward in a sweeping curve, becoming less and less distinct as it reaches the periphery. It cannot be traced to parietal or visceral attachments. These curving linear markings resemble the walls of large emphysematous blebs. Basal lung markings are rather heavy. The structureless area of the left upper resembles an area of localized pneumothorax, but no distinct lung margin is made out. Compressed upper lobe is not made out and there is no displacement of any thoracic structures. Figure 1 demonstrates the X-ray findings. Figure 1a is a graphic representation of the gross findings.

Diagnostic Procedures

Pneumothorax was induced as a diagnostic procedure on July 28, 1931. The idea of the procedure was to demonstrate a lateral lung margin in the apparent structureless area, therefore establishing the fact that the condition

was not one of spontaneous pneumothorax. The pleural space was gained, giving a negative reading of -2 to $-3\frac{1}{2}$, and 400 cc. of air was introduced, which gradually reduced the manometer reading 0 to -1. Subsequent X-ray showed a margin of the left upper lobe in the structureless area as is shown by



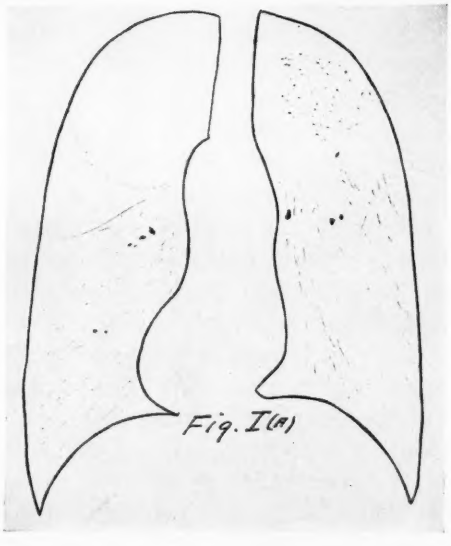
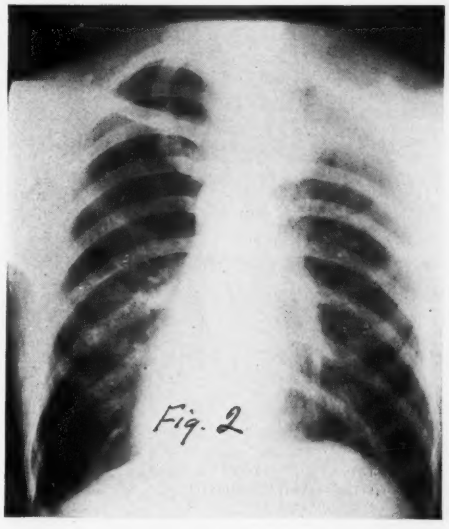
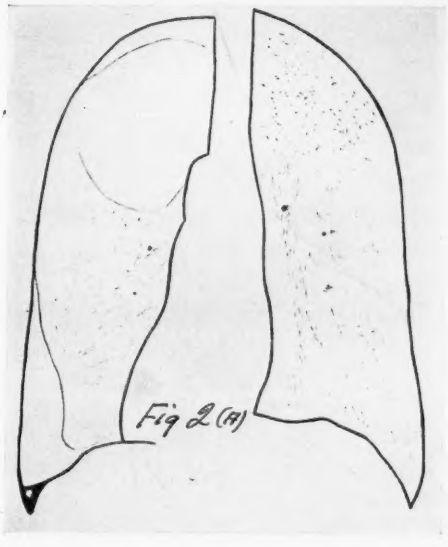


figure 2. Graphic representation of the findings are shown in figure 2a. Figure 3 shows X-ray of the case reported by Wilson. After interpretation of the X-ray findings, air was withdrawn to prevent the possible rupture of one of the large emphysematous blebs with the formation of a valvular type of pleuro-pulmonary fistula resulting in an obstinate spontaneous pneumothorax.

This diagnostic procedure correlated with the clinical picture and physical signs, as well as X-ray findings, resulted in the diagnosis of the upper-lobe pathological finding as one of congenital cystic disease of the lung.

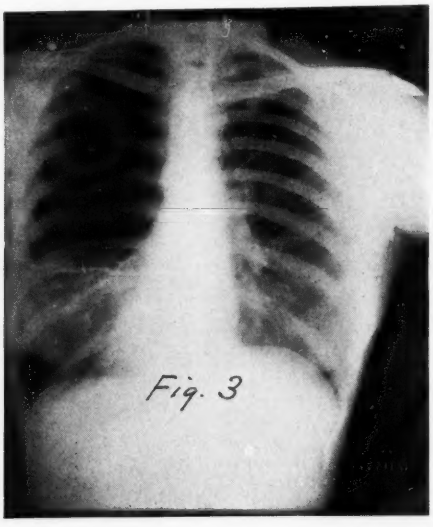




Bronchoscopic Examination: Bronchoscopic examination was made September 1, 1931. No foreign body was demonstrated. No inflammatory reaction was seen. The operator was unable to demonstrate the main

bronchus of the left upper lobe. The operator desired to instil lipiodol into the main bronchus and demonstrate the result by subsequent X-ray, but the bronchial opening could not be demonstrated. This result had been predicted by the clinician, as in these cases of cystic disease the opening is so small that bronchoscopy fails to locate it. This was true of Wilson's case.

X-Ray Findings: (two cases): X-ray findings in the two cases in general are as follows: Both cases are of left-sided cystic disease. The left upper chest presents greater width than the right. The intercostal spaces are increased in comparison with those of the right. Cardiac shadows are somewhat distorted in outline without definite displacement. There is no displacement of the mediastinal organs. There is no distortion or change in the position of



the diaphragm. The left lower lobes in both cases present an exaggeration of normal lung markings. No apparent change in the pleurae.

The left upper thorax in both cases appears remarkably clear, being entirely devoid of any lung structure except for fine strands which divide the clear space of the left upper thorax into ovoid areas of varying size from 3 to 10 cm. in diameter. These dividing strands are fine but dense, resembling in size and density the line of lobar pleurisy so often seen. The chief characteristic of these lines is the fact that they traverse the space in wide sweeping curves, differentiating them from the fiddle-string adhesions traversing a pneumothorax space.

DIFFERENTIAL DIAGNOSIS

In discussing the differential diagnosis of cystic disease we will concern ourselves only with differentiating the condition from that of spontane-

ous pneumothorax. As pointed out by Wilson this condition is, as a rule, diagnosed as such.

The chief differentiating points are:

(a) There is no history of sudden onset.

(b) There are usually no subjective symptoms other than shortness of breath in far-advanced cases.

(c) No pathological change can be demonstrated as an aetiological factor of spontaneous pneumothorax.

(d) X-ray and physical findings remain unchanged over a long period of time.

(e) The condition is accidentally discovered by routine X-ray plate, there being no symptoms referable to the chest.

(f) X-ray findings differ from those of spontaneous pneumothorax in the following respects:

(1) There is no displacement of the mediastinum or of the mediastinal organs.

(2) The compressed lobe cannot be seen.

(3) The fine strands traversing the space are in wide sweeping curves and are not straight as one would expect to find the small taut adhesions traversing a pneumothorax space.

DIAGNOSTIC PROCEDURES FOR DIFFERENTIATION FROM SPONTANEOUS PNEUMOTHORAX

Induction of Artificial Pneumothorax: Thoracentesis of such cases with a manometer reading gives either a normal intrapleural negative pressure or a slightly reduced negative pressure. The introduction of from 300 to 500 cc. of air, with subsequent X-ray, will demonstrate a line of visceral pleura traversing the apparent structureless space. This procedure with X-ray evidence positively excludes the existence of spontaneous pneumothorax. After X-ray is made and interpreted the air should be withdrawn from the pleural sac. This procedure is necessary to prevent the accident of a rupture of an emphysematous bleb with the formation of a valve-type pleuropulmonary fistula resulting in a spontaneous pneumothorax.

Thoracentesis with needle puncture of the structureless space, with injection of from 1 to 2 cc. of lipiodol, with subsequent X-ray will demonstrate retention of the lipiodol by the curving small strands traversing the space. These small curving bands are the walls of the emphysematous cysts and retain the lipiodol within the cyst. This procedure has been done without apparent harm but should not be done if diagnosis can

be confirmed by the induction of artificial pneumothorax, as lipiodol is not expelled from the cysts even after a long interval of time. Bronchoscopic examination of these cases results in the operator being unable to locate the main bronchus supplying the more or less structureless lobe. Bronchoscopic examination should be a routine procedure in all of these cases to eliminate the possibility of partial obstruction from a foreign body or from a tumor mass.

AUTOPSY FINDINGS

Autopsy findings in part, as reported by Hermes and Mumme (2), are as follows:

Autopsy findings of the thorax *in toto* (method according to Brauer and Fahr). Section through the thorax showed the following picture. The whole right upper lobe is attached to the chest wall by adhesions. Its parenchyma is occupied by a system of multiple cavities or cysts varying in size. The inner walls of the cysts are smooth, gray, and interspersed with thin prominent bands. The separating walls between the cysts are not more than 1 mm. in width. The lining of the cysts is smooth and glistening. Histological findings show the absence of inflammatory tissue.

SUMMARY

This disease entity is extremely rare, and is usually accidentally discovered by routine X-ray. It is not to be confused with congenital bronchiectasis. The condition is usually diagnosed as spontaneous pneumothorax, but can be differentiated from it by careful consideration of the clinical picture and by detailed interpretation of the X-ray plate. If other proof is required, artificial pneumothorax may be established, which differentiates the two conditions readily.

REFERENCES

(1) WILSON, J. A.: Amer. Jour. Roent. & Rad. Ther., 1927, xvii, 432.
(2) HERMES, J., AND MUMME, C.: Beitr. z. Klin. d. Tuberk., 1931, lxxvii, 701.

SPONTANEOUS PNEUMOTHORAX WITH ACUTE ABDOMINAL SYMPTOMS

Report of a Case

WALDO R. OECHSLI[1] AND JANE SKILLEN[1]

Spontaneous pneumothorax is a most striking complication of pulmonary tuberculosis and proves fatal in a high percentage of cases. Early diagnosis and treatment are vital. In the patient presenting typical symptoms, no difficulty is encountered, but occasionally the character of the symptoms leads one to suspect some extrapulmonary condition rather than pulmonary collapse.

The symptoms usually associated with spontaneous pneumothorax are acute pain in the chest, dyspnoea, high temperature, rapid pulse and shock. Of these symptoms, dyspnoea is undoubtedly the one most constantly present. Norris and Landis (1) consider it to be the most characteristic feature of spontaneous pneumothorax. Many cases, however, do not present such typical symptoms. The onset may be insidious or some of the symptoms may be lacking. The case here presented constitutes one of the more uncommon exceptions to the rule, in that the predominating symptoms were gastrointestinal, and dyspnoea was practically absent. The case illustrates how one may easily be lead astray by an atypical symptom complex.

Beardsley (2) reported a very similar case in 1911, and remarked on the rarity of abdominal symptoms in spontaneous pneumothorax. The presence of collapse was discovered only at postmortem examination, "The writer being misled by the severity of the abdominal symptoms."

Report of Case

B. B., female, aged 25, entered Olive View Sanatorium on August 20, 1929, with a diagnosis of far-advanced pulmonary tuberculosis. The onset of the disease was in January, 1929, and she had been in bed since May of the same year. On admission, she had physical and X-ray evidence of infiltration above the second rib in the right lung and of infiltration and cavitation throughout the upper two-thirds of the left lung (figure 1). The parenchyma was quite

[1] Olive View Sanatorium, Olive View, California.

free from involvement in both bases but there were many pleuritic crepitations over the entire left base. The temperature ranged from 99.0° to 102.0°F., the pulse from 80 to 120, and the respirations from 18 to 24. She complained of cough, expectoration, weakness, hoarseness and pain over the left base on respiration. She had no dyspnoea and no history of haemorrhage. Throat examination revealed an incipient tuberculous involvement of the larynx. Blood-pressure was 96/62. Urinalysis was negative, sputum positive, leucocytes 21,000, haemoglobin 54 per cent, and blood-sedimentation time 10 minutes. Weight 100 lbs., as compared with normal of 150 lbs.

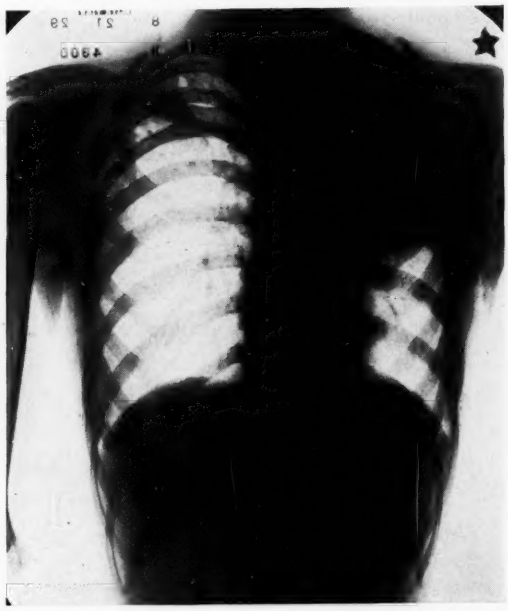


Fig. 1. Appearance of chest August 21, 1929. Tuberculous involvement of the right apex and upper half of the left lung.

During the first three months in the sanatorium, there were no unusual developments. The outstanding symptoms were severe, racking cough and pleurisy at the left base. The patient was nauseated at times and vomited occasionally. This usually occurred after an attack of coughing and was not considered to be of material significance.

The temperature range for the week preceding November 24 was 99.0° to 102.0°F., the pulse ran from 90 to 120 and the respirations from 20 to 24. On the evening of the 24th, the patient had a severe chill, with temperature of 103°, pulse-rate 125 and respirations 28. At 11:00 P.M., she awoke and complained to the nurse of "indigestion and pleurisy." At 2:30 A.M. she again

awoke with severe pain centering in the epigastrium, and nausea and vomiting. Morphine-sulphate, gr. 1/8, hypodermically, gave some relief from the pain but the patient slept very little. She could take no nourishment that day, emesis continued, and sedatives were necessary to control the abdominal pain. There was no noticeable dyspnoea and not a great deal of coughing.

During the next five days there was very little change in her condition. The temperature remained up to 102° and 103°F., the pulse 120 to 136, and respirations 18 to 28, the latter very little faster than previously. The pain in the epigastrium continued with only occasional slight pain in the left side

Fig. 2. X-ray in supine position. Left lung partially collapsed. Heart displaced to right. The diaphragm is depressed far into the abdomen, as indicated by the arrows.

of the chest. There was no dyspnoea. On November 27, she was transferred to the Acute Hospital Unit as a case with acute abdominal trouble complicating far-advanced pulmonary tuberculosis. On November 29, in the course of a physical examination in which the abdominal findings were questionable or negative, extreme hyperresonance over the lower part of the left chest was noticed. The heart was pushed far to the right and there were no breath-sounds over the left base. This side of the chest seemed rather full, with widening of the interspaces. A needle was inserted and air was removed with some relief. X-ray in the prone position (figure 2) showed the left lung to be

partially collapsed. There was fluid present and the heart and mediastinum were displaced to the right. The left diaphragm was pushed far into the abdomen, so that instead of presenting a convex curve upwards, there was a curve with convexity downwards. The lowest part of the diaphragm lay at the level of the first lumbar vertebra.

During the next few days air was removed daily, with great relief of the abdominal symptoms and improvement in general condition. The removed pleural fluid was positive for tubercle bacilli by both direct smear and guinea-pig inoculation. The leucocyte count was 19,200, sedimentation-time 21 minutes, temperature range 98°–102°F., pulse 90 to 120 and respirations 18 to 28. The patient continued to improve and, in time, all abdominal symptoms disappeared.

On February 15, 1930, gomenol (2.5 per cent in olive oil) was injected into the left pleural cavity after withdrawal of the fluid. For several days after this the patient expectorated the oil.

There is little of interest in her further progress. The left lung remained collapsed. The disease progressed in the right lung with cavity-formation. After remaining stationary for a time, the patient grew worse and died July 15, 1931. Permission for postmortem examination was refused.

CONCLUSIONS

The outstanding feature of this case is the absence of the one symptom that is usually present in spontaneous pneumothorax, namely, dyspnoea, and the presence of symptoms not usually encountered in these cases, that is, abdominal pain, nausea and vomiting. It is felt that this variation from the usual symptom-complex is probably explained by the fact that the direction of greatest displacement of viscera was downward, with consequent embarrassment of the diaphragm. The heart and mediastinum were moderately displaced, but apparently not sufficiently to cause dyspnoea.

REFERENCES

(1) NORRIS, G. W., AND LANDIS, H. R. M.: Diseases of the chest and the principles of physical diagnosis, Philadelphia, W. B. Saunders Co., 1929, ed. 4, p. 698.

(2) BEARDSLEY, E. J. G.: Pneumothorax with acute abdominal symptoms, New York M. J., 1911, xii, 183.

FLUOROSCOPY IN TUBERCULOSIS CASE-FINDING[1]

H. W. HETHERINGTON AND E. W. FLAHIFF

Examinations for tuberculosis in Philadelphia (1) (2) and in several other places in the United States (3) (4) have shown that some children in whom disease has not been recognized are attending school with manifest tuberculosis demonstrable by X-ray films and physical examination and that an appreciable percentage have latent disease not demonstrable by physical examination but by X-ray examination only. X-ray films reveal the type, anatomical extent and characteristics of latent tuberculosis of the lungs and tracheobronchial lymph nodes, the recognition of which is essential in an effort to determine the incidence of grave tuberculous infection in any group of persons. The routine application of X-ray examination to all school-children to find those threatened with the development of clinical tuberculosis has only one objection, namely, its expense.

In order to discover, at the lowest possible cost, the largest possible number of children who on further examination will be found to have significant lesions, various methods of selection have been adopted or proposed. One method is to examine every child living in contact with a patient who has tubercle bacilli in the sputum. This procedure is now generally recognized as indicated when such exposure to contagion is known to occur. Children from families harboring open tuberculosis were observed for a period of years at the Henry Phipps Institute (1). Approximately ten per cent developed clinical tuberculosis, 21 per cent had latent tuberculosis of tracheobronchial lymph nodes and 3 per cent latent apical tuberculosis. Chadwick (3) found that reactions to tuberculin indicating infection occurred twice as often in children known to be in contact with tuberculosis as in noncontact children. If all cases of open tuberculosis were recognized and all those in intimate contact given X-ray examination at definite intervals there would probably be little need for examination of noncontact groups, but cases of far-advanced tuberculosis diagnosed only after prolonged illness indicate that contact with unrecognized tuberculosis may readily occur.

[1] From the Henry Phipps Institute of the University of Pennsylvania, Philadelphia, Pennsylvania. Aided by a grant from the Metropolitan Life Insurance Company.

The tuberculin test is frequently used to select children for X-ray examination, especially when a history of contact is difficult to obtain, as in examining school-children. It is well known that many children who have intense reactions do not develop significant disease. Nevertheless, when the intracutaneous method is employed, the highest percentage of dangerous lesions is found among children who react most intensely to the smallest quantity of tuberculin and the incidence of demonstrable tuberculous lesions is progressively less in groups who react less intensely to tuberculin or who react only to the larger quantities. The value of the tuberculin test is greatest in young children because the earlier the age-period the less the probability that a positive reaction has been acquired through casual contacts. For the same reason it is more valuable in rural communities than in a city like Philadelphia, where between 75 and 90 per cent of high-school children from 15 to 19 years of age have positive reactions (5). When examinations are voluntary the objection of many parents and children to the injection may decrease the number who present themselves for examination.

Age, sex and race are significant in the selection of children who should be examined. Manifest and latent apical tuberculosis are not infrequent in adolescent children. They occur much more often in adolescent girls than in boys of the same age and their incidence is considerably higher among negro children than among white (5). The importance of age in interpreting the tuberculin reaction has been referred to.

Fluoroscopy may be used to indicate children who need further investigation. In the United States fluoroscopic examination of the lungs is not commonly believed to be as valuable as examination by means of stereoscopic X-ray films. Its cheapness recommends it when examinations at frequent intervals are required, as in artificial-pneumothorax treatment. Nevertheless, X-ray films taken in different positions, the anteroposterior, the rotated and oblique views (6), supply most of the information that fluoroscopic examination will give and in addition show a wealth of detail not revealed by the fluoroscope. Several writers (7) (8) have pointed out the superiority of roentgenographic over fluoroscopic examination. They cite cases in which the fluoroscope has failed to demonstrate scanty pulmonary infiltration and even thin-walled cavities. Pichard (9) suggests that the variation in detail seen on the fluoroscopic screen and in X-ray films is largely the result of properties of the human eye. Radiographic films are viewed in bright light whereas fluoroscopic examination must be made in a dark room. The nerve impulses initiated

by the action of light on the retina are first received by the layer of rods and cones and transmitted to the nerve-fibres. The visual purple, a photochemical substance associated with the rods, is necessary for vision in dim light. The *fovea centralis*, which is the most sensitive part of the eye, contains cones only and hence is insensitive in dim light. In viewing X-ray films we are able to use this area but in a darkened room the peripheral parts of the eye must be used and accurate detail cannot be seen.

In 1928 Fellows and Ordway (10) and in 1929 Reid (11) reported the results of fluoroscopic examination of applicants for positions in the Metropolitan Life Insurance Company. Of 4,843 persons who were passed on physical examination 59, or 1.21 per cent, were demonstrated by the fluoroscope to have pulmonary pathological changes that after the X-ray films were studied were classed as anatomical tuberculosis. The ages of the applicants were not reported.

In 1930 Kattentidt (12) reported results of fluoroscopic examination of the lungs of 4,836 Munich University students. Fourteen and eight-tenths per cent showed what he regarded as inactive lesions, 1.3 per cent had lesions described by him as partially active, and 0.56 per cent active lesions. Approximately 2 per cent had tuberculous disease regarded as significant.

A COMPARISON OF EXAMINATIONS OF YOUNG ADULTS WITH THE FLUOROSCOPE AND WITH X-RAY FILMS

During 1930–1931 we made fluoroscopic examinations to discover tuberculous lesions of the lungs and tracheobronchial lymph nodes. The first group examined comprised 181 young women between the ages of 16 and 22 years. The results of roentgenographic and fluoroscopic examinations are shown in table 1. Of 163 students appearing normal on the fluoroscopic screen, 150 showed no abnormality in X-ray films, three had pulmonary nodules; four, calcification of tracheobronchial lymph nodes; and six, small areas of tuberculous disease limited to the apex of the lung above the clavicle. In 18 students a tuberculous lesion was suspected with the fluoroscope. Of these, the presence of pulmonary nodules was confirmed in four of six, and calcification of bronchial lymph nodes was found in four of six. Nonapical disease suspected in one case was confirmed, but apical disease suspected in 5 women was not confirmed by X-ray films.

The most disappointing aspect of the fluoroscopic examination was

our failure to detect small and scanty apical involvement, that is, latent apical tuberculosis limited to the lung above the clavicle. On the other hand, when one shoulder is lower than the other and the ribs on one side are closer together, the resulting impairment of illumination on the fluoroscopic screen may cause apical disease to be suspected where it does not exist.

TABLE 1

Comparison of the results of roentgenographic and fluoroscopic examinations of the lungs of women students 16 to 22 years of age

RESULTS OF FLUOROSCOPIC EXAMINATION	NUMBER ROENTGENOGRAPHED, GROUPED BY RESULTS OF FLUOROSCOPIC EXAMINATION	RESULTS OF ROENTGENOGRAPHIC EXAMINATIONS				
		Number negative	Number with pulmonary nodule	Number with calcified foci in tracheobronchial lymph nodes	Number with nonapical tuberculous infiltration of the lung	Number with apical tuberculous infiltration of the lung
Number negative	163	150	3	4	0	6
Number with pulmonary nodule	6	2	4	0	0	0
Number with calcified foci in tracheobronchial lymph nodes	6	2	0	4	0	0
Number with nonapical tuberculous infiltration of the lung	1	0	0	0	1	0
Number with apical tuberculous infiltration of the lung	5	4	1	0	0	0
Totals	181	158	8	8	1	6

In a group of male students between the ages of 20 and 25 years apical involvement was both more frequent and more extensive (table 2). Among 166 students, 25 showed calcified nodules in the lungs or tracheobronchial lymph nodes on X-ray examination. Thirteen of these had been detected with the fluoroscope. Twenty-three had apical infiltrations, of which 10 had been seen on fluoroscopic examination. In this group the fluoroscope showed the diseased area in 5 instances in which it extended below the clavicle, and in five instances in which it was limited to the apex of the lung above the clavicle; it failed to show the infiltration in 2 cases in which the diseased area was situated both above and below the clavicle and in 11 cases in which it was limited to the lung above the clavicle.

It is accordingly apparent that by fluoroscopic observation of the lungs of adolescents and young adults only a part of the tuberculous disease revealed by X-ray films will be discovered. Nevertheless, the cases detected by fluoroscopic examination are likely to be the more advanced and significant instances of the disease, which most urgently require treatment or supervision.

TABLE 2

Comparison of the results of roentgenographic and fluoroscopic examinations of the lungs of male students 20 to 25 years of age

RESULTS OF FLUOROSCOPIC EXAMINATION	NUMBER ROENTGENOGRAPHED, GROUPED BY RESULTS OF FLUOROSCOPIC EXAMINATION	RESULTS OF ROENTGENOGRAPHIC EXAMINATIONS			
		Number negative	Number with calcified foci in lungs or tracheobronchial lymph nodes	Number with nonapical tuberculous infiltration of the lung	Number with apical tuberculous infiltration of the lung
Number negative	131	107	12	2	10
Number with calcified foci in lungs or tracheobronchial lymph nodes	22	6	13	0	3
Number with nonapical tuberculous infiltration of the lung	1	1	0	0	0
Number with apical tuberculous infiltration of the lung	12	2	0	0	10
Totals	166	116	25	2	23

A comparison of the number of lesions detected by X-ray examination with the fluoroscope and with films is shown in table 3. Each lesion is considered separately, so that, for example, a student having a pulmonary nodule with an associated lymph-node lesion and bilateral apical infiltration appears in the table four times, once for the nodule, once for the lymph node lesion and twice for the bilateral infiltration. In the group examined there were 7 apical infiltrations sufficiently advanced to extend below the clavicle. Five of these were detected by fluoroscopic examination. There were 28 infiltrations limited to the apex of the lung above the clavicle, and of these five were detected with the fluoroscope.

An attempt was made to correlate also the density of the shadows of the lesions seen in the X-ray films with the results of fluoroscopic observation. Eight students had unilateral, supraclavicular, apical infiltrations, two of which had been found with the fluoroscope. Of 6 students

with undetected lesions the difference in density between the lesion and the corresponding area of normal lung on the opposite side was regarded as conspicuous in two and slight in four, whereas the difference was slight in both students with lesions discovered fluoroscopically. When the transmission of light through the shadow of the lesion in the X-ray film and through the contralateral area of normal lung tissue was measured electrically (with a densimeter (13)) a similar result was obtained; that is, the difference in density was greatest in two lesions that had not been observed, and was slight in the two lesions that had been observed on the fluoroscopic screen.

TABLE 3

A comparison of the number of lesions detected with the fluoroscope and shown in X-ray films

TYPE OF LESION	SUSPECTED ON FLUOROSCOPIC EXAMINATION BUT NOT DEMONSTRATED IN X-RAY FILMS	NOT SEEN ON FLUOROSCOPIC EXAMINATION BUT DEMONSTRATED IN X-RAY FILMS	SEEN ON FLUOROSCOPIC EXAMINATION AND DEMONSTRATED IN X-RAY FILMS	TOTAL SEEN IN X-RAY FILMS
Pulmonary nodule	4	9	11	20
Calcified foci in tracheobronchial lymph nodes	2	8	15	23
Nonapical infiltration of the lung	1	2	0	2
Supraclavicular apical infiltration	2	23	5	28
Apical infiltration extending below the clavicle	0	2	5	7
Totals	9	44	36	80

Eight students had bilateral supraclavicular infiltrations. In three the lesion on one side only had been discovered with the fluoroscope. In two of these there was no apparent difference in density of the lesions on the two sides, but in one the difference was marked. In the films of the 5 remaining students the difference in density was not apparent in three and only slight in two.

Unilateral apical infiltration extending below the clavicle was seen fluoroscopically in the 3 cases in which it occurred. Four students had bilateral apical infiltration extending below the clavicle on one side only. The more extensive lesion was detected in two instances and in two instances neither was detected.

The density of the lesion is however only one of the factors that determine its visibility on the fluoroscopic screen. Variations in exposure to

compensate for differences in the thickness of the chest-wall can easily be made in taking X-ray films, but similar variations during fluoroscopic examinations are possible only within narrow limits. Also the examiner may make examinations with his eyes less well adapted at one time than another.

EXAMINATIONS OF SCHOOL-CHILDREN WITH THE FLUOROSCOPE AND WITH X-RAY FILMS

The examination of school-children by means of the tuberculin test and X-ray films in the search for those who have dangerous tuberculous lesions encounters certain practical difficulties. One of these is the reluctance of parents and older pupils to consent to the tuberculin test. Another is the considerable cost of the films. In order to avoid these difficulties the use of the fluoroscope suggests itself. This instrument was used in the examination of children in two elementary schools.

The examination usually lasted three or four minutes. During most of this time only a small part of the chest was exposed to X-rays. The child stood facing the examiner with his hands on his hips and his elbows turned forward. Movement of the diaphragm was observed both on quiet and deep respiration. All areas of the lung were carefully scrutinized. The apices were examined with clavicles both high and low, and older children were asked to cough while the apices were under observation. Examination was made while the child rotated himself slowly from side to side. The interbronchial angle was observed obliquely. The same procedure was repeated with the child's back to the examiner.

A total of 953 children were examined and 69 were selected for X-ray films because pulmonary abnormality was suspected. As is shown in table 4, the interpretation of shadows on the fluoroscopic screen was confirmed in approximately 70 per cent. However, the fluoroscopic examination was sometimes cut short when the examiner decided that X-ray films should be taken, and this may in part account for the cases in which only one lesion was seen with the fluoroscope although two were present.

In 1927 we gave tuberculin tests to the children of the same two schools and gave roentgenographic examinations to the reactors. Since no material alteration in the racial or economic status of the children had occurred in the interval the earlier results are compared with the more recent in table 5.

This comparison suggests that a considerable percentage of tubercu-

lous lesions are not detected by the examiner using the fluoroscope, but that more children will be found to have significant lesions among those selected for X-ray examination with the fluoroscope than among those

TABLE 4

Roentgenographic examination of 69 children with lesions suspected with the fluoroscope

TYPE OF LESION	RESULT OF FLUOROSCOPIC EXAMINATION	RESULT OF EXAMINATION BY X-RAY FILMS
Pulmonary nodule	17	14*
Calcified lesion of tracheobronchial lymph nodes	29	21†
Uncalcified lesion of tracheobronchial lymph nodes	3	1
Tuberculous infiltration	15§	8****
Non-tuberculous infiltration	5	6§
Totals	69	50

* Accompanied in 7 instances by calcified lesions of tracheobronchial lymph nodes not recognized with the fluoroscope and in one instance by pulmonary infiltration similarly unrecognized.

† Accompanied in 8 instances by pulmonary nodules, six of which had been recognized on fluoroscopic examination, and in one instance by a scanty infiltration not seen on fluoroscopic examination.

§ One lesion considered tuberculous on fluoroscopic examination was considered nontuberculous after examination (6).

**** Accompanied in one instance by a nodule that had been recognized and a tracheobronchial calcification that had not been recognized with the fluoroscope.

Note: Two children, normal on both fluoroscopic and roentgenographic examination, were given the roentgenographic examination because of cough, and a third child had a density in the neck seen with the fluoroscope and confirmed in X-ray films.

TABLE 5

Selection of school-children for roentgenographic examination by the tuberculin test and by fluoroscopic examination

DATE	NUMBER TESTED WITH TUBERCULIN	NUMBER SELECTED FOR X-RAY EXAMINATION	NUMBER WITH CALCIFIED FOCI IN LUNGS OR TRACHEOBRONCHIAL LYMPH NODES	NUMBER WITH TUBERCULOUS INFILTRATION OF THE LUNGS
1927	1057	367	89	19
	NUMBER EXAMINED WITH THE FLUOROSCOPE			
1931	953	69	33	10

selected by the tuberculin reaction. Of 367 children reacting to tuberculin, lesions were found roentgenographically in 108, or 29.7 per cent, and of 69 children with pulmonary abnormality suspected with the

fluoroscope, in 43, or 62.3 per cent. Thus fluoroscopy appears in a more favorable light when the cost of films in discovering children with latent tuberculosis is taken into consideration.

In order to obtain a more accurate conception of the number and extent of lesions not detected with the fluoroscope, 150 children between the ages of 12 and 14 years, apparently normal on fluoroscopic examination, were given roentgenographic examination. Two of these children had calcified pulmonary nodules, one, 2 mm. in diameter, situated at the right first interspace anteriorly, and the other, 3 mm. in diameter, situated in the middle third of the right lung toward the axilla. Three children had calcified areas in the tracheobronchial lymph nodes. In the first child the calcified area was situated at the interbronchial angle and measured 6 by 10 mm. The second child showed a faintly calcified area, 1.2 by 1.4 cm., at the left hilum, and the third two calcified areas 1 by 6 mm. and 3 by 8 mm., at the left hilum within the shadow of the heart. Of these children 145 were normal on roentgenographic examination.

SUMMARY

The results of the examination of 347 young adults with the fluoroscope and with stereoscopic X-ray films were compared. It was found that the examiner with the fluoroscope frequently failed to detect pulmonary infiltration when limited to the apex of the lung above the clavicle, but in most instances detected more extensive infiltrations. Roentgenographic examination was made of 69 children selected from 953 schoolchildren because pulmonary abnormality was suspected with the fluoroscope; lesions were confirmed in the X-ray film in 43 of these, but in 26 were either not present or considered not to be tuberculous. Among 150 children between 12 and 14 years of age in whom no abnormality was detected fluoroscopically, X-ray films revealed calcified tuberculous lesions in five.

CONCLUSIONS

1. The fluoroscope fails to reveal a considerable part of the calcified nodules of lungs and lymph nodes visible in roentgenographs.

2. Tuberculous infiltration limited to the apex of the lung above the clavicle is seldom recognizable by fluoroscopic examination.

3. Apical infiltration extending below the clavicle is usually recognizable with the fluoroscope, but may be overlooked.

4. The fluoroscope may be used to detect the more extensive and

therefore probably the more significant pulmonary lesions but when fluoroscopic examination does not reveal any pulmonary abnormality the possibility of a significant tuberculous lesion cannot be excluded.

5. Fluoroscopy affords a relatively inexpensive method of selecting children who on further examination will be found to need treatment or prophylactic care for tuberculosis.

6. Lesions suspected with the fluoroscope should always be confirmed in roentgenographic films.

REFERENCES

(1) Opie, E. L., and McPhedran, F. M.: Jour. Amer. Med. Ass., 1926, lxxxvii, 1549.
(2) Opie, E. L., Landis, H. R. M., McPhedran, F. M., and Hetherington, H. W.: Amer. Rev. Tuberc., 1929, xx, 413.
(3) Chadwick, H. D.: Ibid., 1927, xv, 601.
(4) Rathbun, W. L.: Tr. Nat. Tuberc. Assoc., 1927, xxiii, 164.
(5) Hetherington, H. W., McPhedran, F. M., Landis, H. R. M., and Opie, E. L.: Amer. Rev. Tuberc., 1929, xx, 421.
(6) McPhedran, F. M.: Ibid., 1929, xx, 532.
(7) La Querriere, A.: J. Med. & Chir. Prat., 1928, xcix, 34.
(8) Guénaux and Gauillard: Bull. Soc. Radiol. Méd. de France, 1927, xv, 23.
(9) Pichard: Arch. Med. Angers, 1927, xxxi, 68.
(10) Fellows, H. H., and Ordway, W. H. Amer. Rev. Tuberc., 1928, xvii, 201.
(11) Reid, A. C.: Ibid., 1929, xx, 46.
(12) Kattentidt, B.: Ztschr. f. Tuberk., 1930, lviii, 209.
(13) Weyl, C., and Warren, S. R.: Radiology, 1931, xvii, 946.

THE TUBERCULOSIS TRAINED NURSE[1]

JOSEPH WALSH

There are so many differences in the education of the tuberculosis-trained and the ordinary trained nurse that it appears desirable to point them out. Paralleled, some of these differences are:

Ordinary trained nurse	*Tuberculosis trained nurse*
Acquires general knowledge of the care of many diseases.	Acquires expert knowledge of the care of tuberculosis.
Instructed to take no responsibility; on change of symptoms consults physician.	Instructed to accept responsibility for variations in symptomatology which she understands.
Receives specific directions for each day and sometimes each hour.	Receives general rather than specific directions for a week to two weeks.
All instruction is objective.	Having had the disease herself she is in possession of an intimate subjective knowledge impossible to inculcate.
Urged to hold no converse with patient.	Taught to explain to patient reasons for symptoms so as to relieve his mind.
Instructed to make no suggestion to the physician.	Is in a special category on account of having had the disease herself.
Learns how to give nourishment, even though small in amount, making it tasty if necessary.	Learns how to give nourishment in more than ordinary amount even when inadvisable to make it especially tasty.
Ready to give sedatives on slight provocation.	Learns how to encourage sleep without sedatives.
Learns how to take temperature but not always very accurately.	Learns how to take temperature accurately.

The graduate nurse of an acute-disease or general hospital is prepared to care particularly for the common accidents, surgical cases and acute

[1] A lecture to nurses at the White Haven Sanatorium, 1932.

diseases of the community. In training she meets fractures, contusions, lacerations, amputations, surgical conditions from the head to the feet, cancers, lobar and lobular pneumonia, influenza, rheumatism, typhoid fever, syphilis, gonorrhoea, heart and kidney diseases, apoplexy, and ulcers of the stomach and duodenum. Rarely, too, she encounters the common children's diseases, such as measles, whooping-cough, scarlet fever and diphtheria.

Some of these, especially the operative cases, show in addition pulmonary tuberculosis, but so little cognizance is taken of it that her training still remains more theoretical than practical in this regard. As a rule she fails to learn how to combat its contagiousness, acquires a fear of it which is unjustified, and becomes as panicky as a lay person over haemoptysis.

On account of the attending physicians and surgeons visiting the general hospital every day, either in person or through the intermedium of an assistant, and on account of a resident physician anxious to learn being always at hand, there is no necessity for the nurse explaining a symptom to the patient or undertaking anything on her own responsibility. The slightest exacerbation of a symptom, or the appearance of a new one, is called to the attention of a physician who explains it to the patient if necessary and gives the orders for its treatment. It is also true that explanations are only rarely called for, since the patient is frequently so ill, in fact, oftentimes in such a stupor, that he would not appreciate or even understand them. The rule is strongly inculcated that the nurse is to converse with the patient as little as possible, accept no responsibility, and do only what is prescribed.

And this is a wise rule. For not only are physicians at hand to advise about every procedure, but the majority of conditions the nurse encounters are of such a character that inexpert interference could do great harm. Lobar pneumonia is a violent disease of short duration, during which the patient is extremely ill, so ill that he may die within any twenty-four hours. The best nursing is that of noninterference, and one single indiscretion may be serious or even fatal. The same thing is true in many cases following serious operations, when a single indiscretion may prove fatal.

In addition, what the nurse can do for these cases is small in amount and insignificant except in a negative way. It is absolutely necessary that she prevent the sick patient or operative case from leaving bed, and that she prevent his being annoyed by visitors. She must see that he takes the proper amount of liquid, passes the proper amount of urine and excrement, and with as little disturbance as possible.

Since practically all of the cases are of short duration, proceeding rapidly to death or recovery, and since the majority are stricken while in average good health, the amount of nourishment ingested even is not of serious importance. The usual lobar pneumonia case has sufficient fat stored up when he is taken ill, that if he took no nourishment for the ordinary period of his illness, it would not be fatal.

Almost the same conditions prevail when the nurse is on a private case. The physician is calling every day or is at least anxious to call if a symptom exacerbates or a new symptom appears. Even here the nurse is instructed to take on herself no responsibility and indulge in no explanations.

In the private care of tuberculosis, conditions are very different. The patient is rarely very ill and even when ill his intelligence and mental activity are not interfered with. The average tuberculosis patient goes almost to the day of death without impairment of his rational faculties. He recovers or dies very slowly. It is not a matter of days, not even of weeks, but of months.

On account of the duration of the disease the physician is anxious to limit the number of his visits to avoid expense, and, on account of the chronicity, it is unnecessary to call frequently since no change one way or the other can be seen in a short time. Hence, as a rule, the physician limits his visits to once a week or even longer, and in the meantime the nurse is expected to exercise some judgment.

It is quite evident that when something occurs which the nurse does not understand, or which arouses fear or anxiety, she is instructed to call the physician, but when symptoms continue as expected, either in the way of improvement or progression, she continues the usual conduct of the case. As a rule, during this interval between the physician's visits, the majority of symptoms continue with little or no change, though at other times some will improve and others become worse. If the improvement or deterioration corresponds with the expected she continues on her own responsibility without calling the physician. It is only when the unexpected occurs that she is to seek help.

Hence, quite different from the general trained nurse, she must learn so much about the disease that she is able to differentiate between the expected and the unexpected. In contrast to a dilettante knowledge of many conditions the tuberculosis nurse must acquire a technical scientific knowledge of one.

This knowledge must be sufficiently definite that she can explain to the patient the probable cause of a particular symptom and thus prevent

alarm. The usual symptoms of the disease, such as cough, expectoration, vague and wandering pains in the chest, petty blood-spitting, constipation, difficulty in taking food, occasional nausea, restlessness, are all under her care to be relieved or aided.

These symptoms are so common, that she has seen how the physician in charge has treated them before, and should have the knowledge and judgment to institute this regimen again. Without hesitation and with assurance she returns the ambulatory patient to bed, diminishes the nourishment, massages a painful part, applies a hot-water bag, paints the chest with iodine, straps the side, administers a laxative in constipation and aromatic spirits in petty indigestion or belching, or gives an alcohol rub.

She has had, however, special advantages in becoming expert not only in the ordinary ways of theoretical study and the practical care of other patients, but by having had the disease herself. In other words, in addition to her limited field and the observation of about a thousand cases of this one ailment, she has had the opportunity of experiencing in her own person the pulmonary symptoms, gastrointestinal difficulties and the mental impressions of the patient. This gives her a superiority in caring for the disease unknown to the general trained nurse. For even when a general nurse has had typhoid fever, it adds little or nothing to her knowledge since she was in a stupor most of the time.

The nurse who has had tuberculosis has conquered it with all her mental faculties alert and with the capability of observing her personal reaction to each symptom and phase. She is acquainted with the circumstances under which they became better or worse. Having experienced subjectively the various trials and embarrassments, she is able to sympathize in every difficulty, instruct in its amelioration and differentiate a quicksand from a petty pitfall.

The general trained nurse is instructed to follow orders and avoid the slightest deviation. In the hospital, orders may be changed only by the visiting or resident physician; in private practice only by the doctor in charge of the case. In the sanatorium the tuberculosis nurse is instructed in the same way, but with the addition that she is to observe, take cognizance of every order and the reason therefor, so that if necessary she can carry it out on her own responsibility in private practice, where she will have to play some of the part of the resident physician.

The number of different drugs administered by the general nurse is very large; but by the tuberculosis nurse small, so that it is not difficult

to become acquainted with and understand her materia medica. As a consequence she is instructed to scrutinize each drug, learn its use and the reason for its administration at this time.

The story is hackneyed, but it has become so only from the successive repetition almost annually of a new nurse arousing the patient already in dreamland by a rough shake at 9 P. M. to give him the medicine intended as a sleeping draught. To administer a night remedy means the danger of disturbing not only the patient but others about him. The nurse with such little initiative as to make no attempt at learning its composition and reason for administration is lacking in the first elements required in the practice of a profession. It will always remain true that no rule can be made or order given excluding, or even superseding common sense.

Assuredly, however, the most difficult traits to inculcate are common sense, judgment and observation; the observation to note every change in the patient and his surroundings, to have the sense to recognize whether something should be done about it and the judgment to decide.

Recently in a hospital I saw a physician prescribe bromide for a patient to be given three times a day. Though he desired it to be administered after meals, he was such a stickler for exactness that he prescribed it for 7 A. M., 1 P. M., and 6 P. M., because breakfast was at 6:30, dinner at 12:30 and supper at 5:30. A week later the times of dinner and supper were changed to one half hour later, and the nurse, though she ought to have known better, continued its administration at the time set, though it was now before the meal.

Night before last was very warm; in spite of the fact of midwinter it was uncomfortable; yet a new patient put into a private room was left all night with the heat turned on,—he, poor fellow, thinking that might be part of the treatment. The nurse could not have slept in the room herself, yet she failed to recognize it was equally difficult for another. Early this morning it became very cold, but the girls in Ward B washed and changed in a chilly dressing-room because they did not know how and the nurse was too negligent to turn on the heat.

As a physician should miss nothing about the patient or his surroundings, a nurse should never enter a room without noting the individual, the bed, the table, the heat and the ventilation, and it is almost trite to say that, if she fails to find something to note or correct, the chances are there was a film over her eyes.

Another reason for the rule against the nurse talking to patients is that

familiarity tends to lessen authority on the one hand and obedience on the other. This is true, but only if she displays ignorance instead of knowledge, frivolity instead of dignity. When the nurse's explanation is palpably wrong or is at variance with a more plausible explanation of the physician, it is quite evident that credence in future will be withheld. When the nurse's conversation degenerates to gossip or "wisecracks" sympathy is lost and antagonism engendered.

Every teacher is obliged to explain to scholars, yet loses neither in dignity nor influence even when the scholars are older and of different sex. He learns how to be affable without frivolity, cordial without familiarity. When the conduct of the nurse continues conventional and dignified, the attitude of the patient will not change. Encouragement, however, must be given without chattering, explanation without garrulity.

The well-trained nurse learns how to commend without flattery and reprove without petulance or nagging. She is not courteous one moment and rude or tactless the next. She prides herself on good manners, and, when the patient deliberately or through a slip of the tongue complains, or makes what seems to be a complaint to higher authority about something she has done, or has omitted to do, she makes no display of peevishness, but, by her easy and natural apology and future endeavor to satisfy, shows her breeding. A patient justifiably complained to the superintendent of a roach on the floor. When called to her attention, the nurse petulantly made a great display of cleaning out the patient's chiffonier, when the cleaning should have been done in the diet kitchen next door.

"That is a nifty pin," said a fresh patient to a pretty probationer, "I wish you would let me wear it." The probationer made no reply, but that afternoon the supervisor stopped at the patient's bedside to remark quietly: "If the nurse had acceded to your request she would have been expelled immediately. I trust you will not endanger a nurse's career again." This is the proper way of dealing with presumption. You have behind you the authority of the hospital. When something is said or done that is difficult to manage alone it is the part of wisdom to let your supervisor help out. This nurse, by showing immediately that she was unwilling to put up with familiarity, gained the respect of all, and was not subjected to impertinence again.

Food: The difference in the dietary treatment of a patient with an acute disease and with pulmonary tuberculosis is considerable. In the case of acute lobar pneumonia the patient is usually very ill for about a week to

two weeks. The duration of the disease is so short that even if the nourishment is small in quantity there is little fear its lack will prove fatal. On account of the fact that his stomach is badly disturbed by the acute intoxication the patient is disinclined to take food, and on account of being delirious or semidelirious frequently refuses it absolutely. With the desire of getting in some, no matter how small the amount, tempting viands of various kinds and many expedients are tried. Soups, broths, milk either straight or disguised with various flavors, junket, custards, orange-albumin water, are all employed in the endeavor to introduce some food, a large amount not being required.

In a case of pulmonary tuberculosis the duration of the disease is so long that unless the patient ingests the ordinary amount of nourishment or even more he will gradually go under. It is not possible to limit the diet to that which would be satisfactory in an acute disease. The patient must eat and, since the eating must be continued over many weeks, it is useless to consider dainties and delicacies which will be appetizing for only one or several times. Our concern must be with what the patient is most likely to take over a protracted period. For instance, patients who are not fond of milk sometimes ask for it mixed with chocolate to disguise the taste. The amount of chocolate they wish is such that it is practically sure to become nauseating within a few days. Instead of the chocolate promoting ingestion over a long time it has the opposite effect.

As a rule foodstuffs and beverages are most easily taken over a protracted period when the taste is indifferent rather than savory. Sweet dainties are more agreeable once or twice, but pall if taken often. We never tire of water since it is without taste; we eat bread and potatoes daily without disgust for the same reason.

In the majority of cases the way milk can be taken over the longest period is straight,—unadulterated. Efforts to make it more palatable may be successful for a few times, but fail over a long term. Since the patient has frequently lost twenty, thirty and sometimes even forty per cent of his weight and this is gained only slowly over a long convalescence, nourishment must be in such amount that gain in weight will be produced and of such a character as to be taken till success is achieved.

A nurse should know how to encourage a patient to eat by instruction and, on account of her previous tuberculosis, by personal example. A patient has told me of a nontuberculosis trained nurse saying, on handing him a glass of milk, that she did not know how he took it,—that if it were she, she was confident she would have to die if milk were necessary.

It is quite evident this nurse with her total lack of knowledge of psychology missed her calling.

Narcotics: In a general hospital when a patient suffers from insomnia due particularly to pain, like that of a broken leg, or of a surgical operation, the physician frequently prescribes opium without hesitation, since the pain is expected to be of short duration and the prescription need not be repeated, or at most not more than several times. The same is true of the insomnia of great restlessness in connection with lobar pneumonia or other infection; opium is justifiable since it will probably be required only once or several times and the patient is too ill and usually in too much of a stupor to know what is being done.

In pulmonary tuberculosis the question of a hypnotic is much more serious. The patient is in full possession of his rational faculties, and when given it once or twice comes readily to demand it frequently. When his insomnia is due to a severe pain like that of a sudden pneumothorax or pleurisy, likely to pass away in twenty-four or forty-eight hours, opium may be justifiably prescribed, but, when the insomnia is due merely to an overactive mind or even a distressing cough, other means should be tried. The objection to opium and its derivatives is that they lessen bronchial secretion, thus preventing proper expectoration; they impair the appetite and disturb digestion, thus increasing decline.

To give a narcotic for plain insomnia is never justifiable. Personally I have never seen a tuberculosis patient improve while continuing to take opium for any cause, though I have seen many improve while complaining of sleeplessness. My experience during the past twenty-nine years with morphia, codeine, heroin, veronal and similar drugs, in cases which appeared to require something, was always bad, since either the narcotic had to be gradually increased and the patient made an addict, or if stopped he had the same difficulty with his insomnia as in the beginning.

As a consequence, special effort should be expended on teaching the patient how to induce sleep apart from drugs. In early manhood, while possibly suffering from an incipient pulmonary tuberculosis, Dr. William Pepper, later in life the great Provost of the University of Pennsylvania, experienced such insomnia that, learning he could sleep on a moving train, he was occasionally constrained to take the night express for Pittsburgh and return the next day. Finding this both overexpensive and time-consuming, he proceeded to study out the conditions of mind and body

conducing to sleep, and learned them so well that for the rest of his life he could sleep at any time in the twenty-four hours when the need and occasion arose.

He studied the posture of his body, the most satisfactory disposition of arms and legs and the position of the head contributing to perfect restfulness, as well as the thoughts to be encouraged or discouraged. Learning that the last act before falling off was an unconscious upward turn of the eyeballs, he acquired the capability of doing this consciously.

In a similar way the patient should be urged to study himself, so as to learn the most comfortable arrangement of the pillows, bed-clothes, the lie of the body and limbs, and the thoughts to encourage or refuse. In addition, the nurse should insist on absolute quiet throughout the house, the proper darkening of the room (some patients wishing more light than others), proper ventilation, fresh sheets carefully spread, not crumpled, head neither too high nor too low and exactly the proper bed-clothes, neither too much nor too little, overmuch being commonly the fault. Oftentimes a glass of milk, a glass of water, a glass of lemonade or orange juice, or again an alcohol rub will help.

Laboring men after a day's work are usually so physically fatigued that even exciting or distressing thoughts fail to prevent sleep. Patients on rest, and the majority of us in sedentary occupations especially when approaching old age, have not the opportunity to become fatigued and agitating thoughts disturb us. My own experience is that too interesting and worrisome thoughts must be avoided, such as serious thoughts about the outcome of the disease, painful thoughts about our physical or financial misfortunes and even too pleasurable thoughts about a successful piece of work. The thoughts tending to quiet the mind are those of an indifferent nature, somewhat toward the pleasurable yet not too much so, something in the fashion of an indifferent day-dream, pleasant to have happen without the pleasure produced being sufficient to excite or agitate.

Run-down patients with tuberculosis frequently come on the first visit complaining of insomnia, on account of which they have been remaining up later and later at night in the hope that fatigue will bring about a change. The late hours are usually spent at an exciting game of bridge or in animated conversation, thereby activating the mental processes. Not only have they met with no success, but the insomnia is aggravated.

Such insomnia is usually corrected by rest. When these patients retire

not merely earlier at night, but take an additional hour in the afternoon, they sleep better. For the more the mind is exercised immediately before retiring and the greater the number of hours of mental work, the more excited it becomes, and as a consequence the more difficult to calm or distract.

Tuberculous activity in the lung produces *per se* no pain, yet during activity and convalescence, and more especially the latter, pains in the chest and elsewhere over the body are not uncommon. These pains change location, and come and go. They may be of any degree, from vague passing twinges to so severe as to prevent sleep, yet without influence antagonistic to convalescence. In the chest they are sometimes associated with thickened pleura and resemble the pain in a joint, the serous membrane of which is thickened following cure of acute rheumatism.

When a patient complains of pain or soreness, the proper procedure on the part of the nurse is first to exclude inflammation by taking the pulse and the temperature. If these are elevated it is quite evident the physician should be notified. If the pulse and temperature correspond to the usual the next step is to inspect the part and the neighborhood. Never express an opinion as to the insignificance of a pain without inspecting the site. More than once I have found when least expected a herpes zoster or a small boil. If nothing is found, compare this with the corresponding part on the opposite side of the body. Learn by touch whether the pain or soreness appears to be superficial or deep. Learn if it occurred before, and if it has been seen and treated by the physician. If for what appears to be the same thing the physician previously prescribed a hot-water bag, painting with iodine, or strapping with adhesive plaster, any of these may be repeated on your own responsibility. If amelioration is not accomplished the physician is to be notified.

For these pains narcotics are not to be thought of, since they can usually be relieved by simple measures or the patient encouraged to put up with them on proper explanation of their insignificant character. It has been well said that he who prescribes narcotics on such slight provocation is practising medicine indolently.

It is true that for some days, or even several weeks, previous to death, the patient may suffer from a painful bowel condition or an agonizing laryngeal tuberculosis when opium in some form becomes a necessity even to the extent of frequent repetition. In this case, however, we have reached the stage when we consider cure impossible and are only con-

cerned with comfort. Yet a fatal prognosis should only be allowed after repeated and strenuous attempts at cure without resort to opium.

Temperature Taking: In acute diseases the nurse is obliged to stand by while the thermometer is in the patient's mouth on account of the danger of swallowing it in stupor, or grinding it under the teeth in delirium. Owing to the number of temperatures to be taken, she must conserve her time and endeavor to take them without unnecessary delay. The common clinical thermometers are made so as to register the temperature in one minute provided the conditions under which it is taken are ideal. The ideal conditions are an acute disease in a robust subject in an enclosed room. The longer the disease lasts, the more run-down the patient, the more the mouth is exposed to cold air, the longer will be the time necessary.

Though the temperature taken by the acute nurse in her rapid way is usually correct, an error of one-fifth to three-fifths of a degree is not infrequent. In a case with high temperature, 103° or over, this error is usually of little importance; in a case of tuberculosis in which the entire elevation may be only two-fifths to four-fifths of a degree, the error is more serious.

In tuberculosis the patient's mental faculties are as perfect as in health and there is no necessity for the nurse standing by to watch him during the taking of the temperature. As a consequence, in a tuberculosis ward the nurse comes to the door and announces temperature-taking time. Each patient puts his own thermometer in his mouth, the nurse goes about the ward and records the pulse and respiration of all, and only then removes the thermometer from each mouth to record the temperature. In this way the thermometer remains in for about ten or more minutes, and in run-down tuberculous cases this length of time is necessary. In fact, in a case in which the exact temperature is of major importance, the nurse should allow the thermometer to remain in the mouth for ten minutes, remove it and look at the record, return it to the mouth for another five minutes and, if the mercury has risen over the previous record, the thermometer should be returned to the mouth for another five minutes, repeating this procedure till the mercury remains stationary.

THE COSTA AND RED-CELL SEDIMENTATION REACTIONS IN LARYNGEAL TUBERCULOSIS

A Comparative Study

CHARLES L. RUBENSTEIN[1]

Not the least of the problems that confront the physician working with clinical tuberculosis are the difficulties that surround the diagnosis of pulmonary activity and the accurate evaluation of the body's defensive forces.

The phthisiolaryngologist in particular finds these two problems disturbing. It is highly important that he secure reliable data regarding the status of the patient and his defensive reserves, as the more active therapeutic measures, such as electrocoagulation, electrocautery, curettage, amputation of the epiglottis, etc., can be employed only in the presence of a favorable and clearly defined immunobiological index.

An instructive case was reported by Dr. Petzahl at the Medical Congress of Hamburg in 1926. The case was that of a young physician, examination of whose larynx had revealed a thickening of one of the false vocal cords. A biopsy was performed. The day following the biopsy the patient's temperature rose suddenly and his condition grew alarmingly worse. A miliary spread in the larynx and a pronounced reactivation of the pulmonary process followed, and the patient succumbed shortly. It is highly probable that, had the patient undergone a careful serobiological study prior to the biopsy, the findings would have contraindicated this surgical measure and the fatal consequences been avoided.

In recent years the necessity of understanding the patient's defensive powers and determining the presence of an active pulmonary process has come to be recognized more and more in the clinic of laryngeal tuberculosis.

There is no doubt that the blood findings are of great importance in this connection, and the intense interest that is shown in all attempts at solving these problems by blood analysis is easily understood.

The blood reactions now in common use can be said to fall into two

[1] Duarte, California.

general classes, the specific and the nonspecific. In the specific group we have the reactions based upon complement-fixation by specific antigen (Besredka, Wassermann, Calmette, Boquet, Negre, Bruck, Petroff, etc.); upon agglutination (Bordet, Fornet, Arloing, Courmont, etc.); precipitation (Hollander, Bonacorsi, etc.); opsonic-index (Wright, etc.). It has been found however, that these reactions are not always infallible guides, as a large number of positive reactions are obtained in cases complicated by syphilis, malaria, leprosy, and convalescence after diphtheria. (Rabinowitsch, Bronfenbrenner, Sachs, Klopstock, Heinmann.)

Among the specific methods of diagnosing tuberculosis, the most reliable reaction is that of complement-fixation. This was first introduced into tuberculosis practice in 1901 by Widal and Le Sourd. Then for some time it fell into oblivion. It is only recently that it has come back with increased popularity, due mainly to the work of Bezredka and his pupils in France, Wassermann in Germany, and others.

The other serological reactions, using specific antigens, such as agglutination, etc., do not have great diagnostic value, since they do not produce unmistakable results.

The nonspecific group includes the reactions based upon the change in the relationship between albumins and globulins. These reactions offer a method of establishing the increased colloidal inconsistency of the blood-serum, as found in diseases that are accompanied by an intense decomposition of blood cells. Several methods have been recommended for ascertaining these changes in the blood-serum, among which we might mention those of Frisch, Daranyi, Matéfy, Sachs, Klopstock and Mündel.

The phenomenon of red blood cell sedimentation observed by Fahreus and introduced into tuberculosis practice by Westergren, Katz, and others, works along the same lines as the nonspecific serodiagnostic methods just mentioned. The sedimentation test, however, offering as it does a simple and easily accessible method, has gained the wider recognition.

The nonspecificity of this reaction, on the other hand, its proneness to react promptly in the presence of intercurrent factors that are sometimes quite harmless to the body, and the absence of a strict border which would permit the differentiation between normality and disease,—these are the factors which tend to impair the value of the reaction.

Tuberculosis practice has been enriched in recent years by a new reaction based upon the biological resistance of the patient. We refer to

the Costa reaction originally introduced for the diagnosis of pregnancy, but later employed also for diagnosing infectious diseases, especially tuberculosis and syphilis. The literature dealing with this reaction has been confined for the most part to Italian medical publications.

The Italian authors, Vercelli and Bagliani, who were the first to apply the Costa reaction to clinical tuberculosis, have been enthusiastic in their reception of it. They are of the opinion that it may be used to good effect not only as a diagnostic method but also as a prognostic test. Gorsonello, on the other hand, is somewhat disparaging in his estimation of the reaction and ascribes neither diagnostic nor prognostic virtues to it.

In view of the scarcity of facts and the differences of opinion that exist with regard to this reaction, we essayed a determination of its practical value for determining the presence of activity and for estimating the biological resistance of the organism, taking as an object for our observations 75 cases of pulmonary tuberculosis, with the complication of laryngeal tuberculosis, at Sawtelle, and at the Los Angeles Sanatorium. We further attempted a comparison of this reaction with the sedimentation reaction.

Requiring a classification of laryngeal tuberculosis that would consider both the laryngeal affection and the pulmonary process, we grouped our material into four classes, according to the classification introduced by the All Russian Convention of Laryngologists in 1924.

In the first class we placed cases with pathological involvement of the soft tissues of the larynx (the so called internal forms) of a productive, infiltrative or ulcerative type, and a mild or inactive form of pulmonary tuberculosis. There were 21 cases in this group.

The second group comprised cases of productive, infiltrative, ulcerative or exudative laryngeal tuberculosis of the internal type with an active subcompensated form of pulmonary tuberculosis. Ten of our cases belonged to this group.

In the third were placed cases with involvement of the cartilaginous ring (the so called external forms) of a productive, infiltrative or ulcerative type and a mild or inactive form of pulmonary tuberculosis. There were 18 cases in this group.

The cases of exudative, external laryngeal tuberculosis with a far-advanced active pulmonary process went into the fourth group. The number of cases in this group was twenty-six.

In the last two groups were also included mixed forms of external and internal involvement, those of exudative type with active pulmonary tuberculosis being placed in the fourth, and all others in the third group.

The technique employed was that suggested by Costa, and modified by Rubenstein and Schwartz. The tip of the finger previously cleaned with alcohol and ether is stabbed with a microcapillary, when 100 mm. of blood is transferred to a glass tube containing 1.5 cc. of 2 per cent novocaine prepared with physiological salt solution, and 100 mm. of 5 per cent sodium citrate. The mixture is then centrifugated for 5 to 8 minutes until there is a complete clearing of the supernatant fluid. After this one drop of pure formalin is added to the tube. If the reaction is positive, we see in the lower third of the tube during the next fifteen minutes a grayish, cloudy sedimentation resembling tobacco-smoke, which later becomes more intense, depending upon the vigor of the reaction. In nonpathological cases the same cloudiness will appear, not before fifteen minutes.

In order to obtain a more exact estimation of the reaction, we divided it into three gradations: (1) strongly positive if the cloudiness appears during the first three minutes; (2) positive if it appears within more than three but less than ten minutes; and (3) doubtfully positive if it appears within more than ten but less than fifteen minutes.

We drew sufficient blood into our capillary for both the Costa and sedimentation tests.

The number of Costa and sedimentation tests made totaled 125 of each. In cases in which the electrocautery was applied, the tests were repeated three times,—before and after the cauterization, at intervals of three, five, and seven days.

It was noted that while in only two of these cases there was a negative Costa reaction, there was on the other hand a comparatively large percentage of normal or nearly normal sedimentations. This was true particularly of the first group of cases, and would seem to point to a greater sensitivity in the Costa reaction.

In the more gravely infected cases, notably of the fourth group, there was a complete parallelism between the two reactions. A close parallelism was also noticed in the second and third groups.

Included in the first group were 2 cases with a doubtful diagnosis of laryngeal tuberculosis. In both there appeared to be a diffuse hyperaemia of the true vocal cords. It was difficult to state whether we had before us a simple laryngitis or specific disease of the larynx. Repeated examinations gave a mildly positive Costa reaction and a slightly accelerated sedimentation of erythrocytes. This fact established for us the diagnosis of nonspecific laryngitis, since, according to our observations, the complication of the primary lung process by involvement of other

parts, especially the larynx, will give a stronger reaction. This last does not hold true, we have found, when the complication is a bone tuberculosis (Rubenstein, Schwartz).

A remarkable influence upon the intensity of both reactions was noticed in two cases after the introduction of artificial pneumothorax and phrenicotomy.

Case S: Male; 25 years of age; ill since February, 1928; entered the Los Angeles Sanatorium December 24, 1928. *Diagnosis:* Far-advanced, bilateral, pulmonary tuberculosis of an exudative type. The first symptoms of a tuberculous involvement of the throat became visible in June, 1929. The patient complained of hoarseness, and examination revealed a hyperaemia of both vocal cords with ulceration of the free edge of the left. The Costa and sedimentation reactions taken at this time were +++ and 48 mm. respectively. The treatment of the larynx was of a strictly conservative nature, consisting of absolute silence, spraying, and instillation of menthol. On June 23, 1929, a right phrenicotomy was performed, and on July 6 of the same year a right artificial pneumothorax was induced. When discharged on December 24, 1929, the patient's larynx was healed, all objective and subjective symptoms having completely disappeared. The Costa and sedimentation tests taken just prior to this discharge were negative and 16 mm. respectively.

Case M: Male; 21 years of age; ill since February, 1929; entered the Los Angeles Sanatorium March 19, 1929. *Diagnosis:* Far-advanced, bilateral, pulmonary tuberculosis, and ulcerative tuberculosis of the larynx. The treatment of the throat consisted of strict silence and spraying with menthol. On March 26, 1929, a right artificial pneumothorax was induced. Three months later, on June 18, 1929, a right phrenicotomy was performed and the artificial pneumothorax discontinued. The Costa and sedimentation tests made a few days prior to the phrenicotomy were +++ and 36 mm. respectively. On May 10, 1930, the patient was given a left artificial pneumothorax and on December 27, 1930, he developed a spontaneous pneumothorax on that side. Following this the patient improved rapidly and, when examined in January, 1931, the condition of his throat approached the normal. The Costa and sedimentation tests made at that time gave + and 12-mm. readings.

Pneumothorax and phrenicotomy, in so far as they have a beneficial effect upon the immunobiological properties of the organism, undoubtedly exert a favorable influence on tuberculosis of the larynx. This favorable influence would be reflected in the results of serobiological tests.

We are fortunately in a position to prove definitely by actual clinical

cases that merely by the performance of phrenicotomy in unilateral cases a complete cure of the pathological condition of the throat resulted simultaneously with the improved conditions of the lungs.

We have observed similar results following thoracoplasty and the newly introduced apicolysis with resection of the first rib. In the opinion of the author, tuberculosis of the larynx widens the indications for these surgical measures.

Particularly striking were the findings of the blood tests of a middle-aged woman, Mrs. Ch., presenting a far-advanced active involvement of the whole right lung with findings in the throat as follows: acute stage of laryngeal tuberculosis, characterized by a profuse infiltration of both false and true vocal cords, the former having reached the stage of ulceration, with a wide spread of reactive inflammation throughout neighboring tissues of the throat. The temperature was 100°–103°. The patient had been coughing a great deal, experiencing pain along with irritability and extreme discomfort of the throat. This was followed by dysphonia which finally developed into complete aphonia. The blood tests revealed the sedimentation on September 5 as 66 and the Costa reaction on September 5 as highly positive. Thoracoplasty was done on October 11, 1931, on the right lung, following a right phrenicotomy on September 13, 1931. Fourteen days after the first stage of the thoracoplasty the patient started to regain her voice, all subjective symptoms slowly diminishing in severity.

I wish to emphasize that the throat in such cases represents for the phthisiolaryngologist a true mirror upon which the conditions and changes of the patient's lungs are reflected. There is a direct interrelationship between the tuberculous process in the lungs and throat. Recession of the process in the lung or reduction in activity by means of collapse therapy is rapidly and accurately reflected by changes of a similarly benign nature in the involved portion of the larynx. Repeated consecutive examination of the larynx of our patient revealed a gradual disappearance of all previously pathological findings. This improvement was going on with such celerity that a figurative comparison with ice melting in the sun would be fully permissible. The remarkable metamorphosis in the patient's throat condition was reflected in the blood tests. The sedimentation test gave a decrease of 32 mm., that is, from 66 it became 34, while the Costa came back from the highly positive to the slightly positive group.

This again proves the greater sensitivity of the Costa reaction in comparison with that of the sedimentation reaction.

In the same manner, the cautery, which eliminates areas of toxicity from the system, can be added to the group of remedies which diminish the intensity of the reaction. In 8 cases in which the electrocautery was applied, a marked slowing up in both tests was observed.

In doubtful febrile cases, in order to ascertain how the organism would react to the cautery, we applied a preliminary experimental cautery, making the Costa and sedimentation tests before and after.

An odd phase of the Costa reaction was observed in a case of widespread bilateral pulmonary tuberculosis with much destruction of the larynx and marked ulceration of both tonsils. The patient suffered a great deal from dysphagia, and the intake of food, both solid and liquid, was accomplished only with the greatest difficulty.

With the approval of staff members at the Soldiers' Home we performed a bilateral injection of 80 per cent alcohol along the superior laryngeals. The effect was surprisingly favorable and lasted for almost two months, during which time the patient was able to eat and drink without experiencing pain. The symptoms of dysphagia reappeared in the ninth week, however, and the tonsillar process spread over the fauces. The patient died shortly afterward.

An interesting feature of this case was found in the fact that a Costa reaction taken two days before the patient's death gave a negative reading, whereas the same reaction taken prior to the injection of alcohol was markedly positive. The probable explanation is that this reaction is inclined to become negative shortly before death. Similar instances have been reported in the current medical literature.

The sedimentation tests taken at the same time as the Costa tests showed no appreciable change, that taken before the injection of alcohol giving approximately the same reading as the one taken two days prior to the patient's death.

Purely by accident, two cases of asthma were included among the cases observed. Both gave negative Costa and sedimentation reactions. This may prove to be important in the differential diagnosis from pulmonary tuberculosis.

It is of course impossible to reduce the biological peculiarities of as complex an organism as a human being to a single simple reaction. Tuberculosis, which, by its nature, has an extremely varied course with each individual, can hardly be classified within definite borders. It would lead to error and disappointment if we were to seek an understanding of the mysterious course of the disease at the bottom of a test-tube. We

must keep in mind that these biological reactions acquire significance only when considered in connection with other laboratory and clinical findings.

These conclusions may prove of great value in the future understanding and treatment of tuberculosis of the larynx. They have been made possible by the close coöperation between the chest and throat clinics at Duarte and also by an intelligent selection of cases for surgery.

CONCLUSIONS

1. An evaluation of the Costa reaction and a comparison with the red-cell sedimentation reaction are presented, the material used for this purpose being 75 cases of pulmonary tuberculosis complicated by laryngeal tuberculosis.
2. Before instituting any radical form of treatment it is highly important that the phthisiolaryngologist secure accurate data regarding the patient's pulmonary process and his immunobiological status.
3. The author recommends as a determinant of pulmonary activity, in addition to sedimentation reaction, the Costa reaction.
4. The Costa and sedimentation reactions disclosed a complete parallelism in cases of far-advanced disease. In latent cases and those with moderately advanced disease there was a disparity between the two reactions that favored the Costa in sensitivity.
5. Both reactions were found to be of value in differential diagnosis between simple and tuberculous laryngitis.
6. Tuberculosis of the larynx widens the indications for chest surgery which, when applied at the proper immunobiological phase, is a most powerful weapon in effecting a complete cure of laryngeal tuberculosis.
7. It is our opinion that the Costa reaction may be employed profitably in the laryngeal-tuberculosis clinic as an objective method for decision as to activity and as a guide in the treatment to be employed.

I want to thank the Medical Staff of the Los Angeles Sanatorium, Duarte, California, and Colonel James A. Mattison, Chief Surgeon of the National Military Home at Sawtelle, California, through whose assistance and coöperation this review of my work was made possible.

BIBLIOGRAPHY

COSTA: Riforma Med., 1923, xxix.
BAGLIANI: Polie Sez Practica, 1923, li.
CORSONELLO: Riforma Med., 1925, ix.

RUBENSTEIN AND SCHWARTZ: Problems of tuberculosis, 1928.
RUBENSTEIN: California & Western Med., 1930, v.
HAJEK: Wien. med. Wchnschr., 1930.
DWORETZKY: Ann. Otol., Rhin. & Laryng., 1930.
SCHWARTZ AND RUBENSTEIN: Vrachebnoe Delo, 1928.
RUBENSTEIN: Amer. Rev. Tuberc., 1931.

A PROTEST AGAINST THE CURRENT CONCEPTION OF ACTIVITY IN PULMONARY TUBERCULOSIS

LOUIS H. FALES[1]

Many of our old misconceptions in regard to pulmonary tuberculosis have been eradicated, but in some quarters our understanding as to what constitutes activity has not kept pace with our other advances.

The conception of activity as viewed by many at the present time is dependent on constitutional symptoms. Elevation of temperature, rapid pulse, loss of weight, malaise, etc., are the criteria. This view of activity is much the same as that held a generation ago. It is the purpose of this paper not only to point out the unreliability of this method, but also to challenge the use of groupings of signs and symptoms for the purpose of diagnosis as advocated by some.

When the rest cure was first instituted, it was found that, when tuberculous patients with constitutional symptoms were placed on continuous rest in bed for a few months, a great change usually occurred. The patients gained weight, temperature and pulse became normal, and all symptoms disappeared.

This rather startling metamorphosis caused clinicians to believe that pulmonary tuberculosis was easily cured, and after a short period of treatment they considered such cases arrested. The introduction of the roentgen-ray, however, demonstrated conclusively that absence of constitutional symptoms had but slight bearing on activity. It became evident that, although clinical symptoms may disappear rapidly, the tuberculous process in the lung often clears and heals very slowly, and usually only after years of prolonged and continuous rest.

Much has been written during the last few years in regard to latent pulmonary tuberculosis in children. Although many of these children have not lost weight, have no elevation of temperature and no physical signs, serial radiographs show not only extensive parenchymal infiltration but often rapid progression or retrogression of the disease. Such lesions, therefore, are markedly active, elevation of temperature, rapid pulse, etc., being late manifestations.

[1] Veterans' Administration Hospital, Livermore, California.

What is true of children is also true of secondary tuberculosis (Ranke (1)); or, in other words, beginning adult tuberculosis. Redeker's (2) teaching that the beginning of adult tuberculosis is an exudative infiltrate, usually found in some portion of the lung below the clavicle and not in the apex, must be considered in this connection. He emphasizes the fact that, on account of its location, the lesion appears without physical signs; also, that the symptoms are either absent or only slight and transient, allowing recognition only by the roentgen-ray. Later developments show these lesions developing on allergic soil to be markedly active, either progressing or retrogressing rapidly, and often with cavity-formation, before constitutional symptoms develop sufficiently to show that the patient is really ill.

It is apparent therefore that absence of constitutional symptoms is not at all unusual when activity exists. Although the presence of constitutional symptoms may be considered a manifestation of activity, conversely we must not conclude that the absence of constitutional symptoms means no activity. In fact it appears that constitutional symptoms as a manifestation of activity most often appear when there is an extension of the tuberculous lesion and they are usually absent when the lesion is stationary or retrogressing.

A generation ago, and even later, râles were considered conclusive evidence of active pulmonary tuberculosis. At the present time, although râles are present in many types of tuberculosis and are of diagnostic value, they do not necessarily indicate an active lesion. The most usual type of râle found in pulmonary tuberculosis, the one heard in showers following expiratory cough, is now regarded as of atelectatic origin and not due to moisture. Their presence over a portion of the chest simply means a partial collapse of alveoli or lobules due to pressure by contraction of fibrous bands, pleural adhesions, or areas of tuberculous infiltration as the case might be.

According to Heise (3) râles are found in only 29 per cent of minimal and 65 per cent of moderately advanced cases of pulmonary tuberculosis. They are seldom heard in the early exudative types, not only because the infiltrate is centrally located, but also because the rapid engorgement of the lung parenchyma, which, becoming organized, prevents the collapse of the alveoli and lobules.

At one time positive sputum was the main criterion for diagnosing active pulmonary tuberculosis. It is still considered of value as a positive finding in advanced tuberculosis, but is of no value in the diagnosis of early cases, before caseation, softening and rupture into a bron-

chus takes place. As a negative finding the importance of the absence of positive sputum seems to be overemphasized by some at the present time.

In 1923, some members of the Saranac Lake group (Heise and Brown (4)), realizing the inadequacy of methods of diagnosis, made a study of the physical signs, symptoms, and laboratory findings of one thousand consecutive cases of pulmonary tuberculosis admitted to Trudeau Sanatorium. From this investigation, the well-known five points for the diagnosis of pulmonary tuberculosis were evolved: (1) wet pleurisy, (2) definite haemoptysis of drachm or more, (3) râles, (4) bacilli in sputum, and (5) parenchymal roentgen-ray lesion.

Bacilli, when found to be present, were considered good evidence of the disease. Of the other points, however, one taken alone was only suggestive evidence of tuberculosis, two points being required for a positive diagnosis. Subjective symptoms, such as elevation of temperature, rapid pulse, and loss of weight, were not used as a basis for diagnosis of the disease itself but for the determination of activity of the lesion.

The Veterans' Administration (5) has for some years been using a group of findings similar to the Saranac Group for the diagnosis of active pulmonary tuberculosis. The group is as follows:

A: Sputum positive for tubercle bacilli.
B: Pleurisy with effusion, without other obvious causes therefor.
C: Authentic haemoptysis.
D: Cavity or pneumothorax diagnosed by stereograms and physical findings.
E: Typical indeterminate, localized, moist râles in the upper lobes, increased or manifested on the first inspiration after a forced expulsion followed by a cough.
F: Parenchymal roentgen-ray lesion as cottony densities, cirrus clouding, etc.
G: Definite toxaemia of probable tuberculous origin manifested by one or more of these symptoms: fever, loss of weight, rapid resting pulse.

Any two of the above findings *A* to *G* establishes the diagnosis of active pulmonary tuberculosis, but, of the list of findings, the first three, *A* to *C* inclusive, are held as relatively more important; any one of the said first three will be considered acceptable evidence of active pulmonary tuberculosis in the absence of any other cause which would explain its exhibition.

At the time of their adoption the above criteria were no doubt a distinct step in advance, but at the present time they do not fit in with our recent views of tuberculosis.

As stated above, it has been found that the childhood type of pulmonary tuberculosis and the secondary adult type, as described by Assmann (8), Redeker (2), and others, and now considered beginning adult tuberculosis, can only be diagnosed by the roentgen-ray, as the infiltration is accompanied by only slight or no constitutional symptoms and usually no physical findings. Bacilli are also not found in the sputum until a breaking down of lung tissue occurs.

In neither the Saranac nor the Veterans' Administration criteria is the roentgen-ray given sufficient importance to permit diagnosis of these types of tuberculosis. It is required that a positive radiograph be linked with another criterion, such as râles or a positive sputum, etc., in order to give it sufficient weight. It is therefore very evident that, if we are to diagnose the types of tuberculosis mentioned, we cannot follow the above criteria. We must give more prominence to the roentgen-ray. It must be made preëminently important; so much so that roentgen-ray shadows as seen on an X-ray film may be considered acceptable evidence of active pulmonary tuberculosis, that is, provided the densities are typical and not explained by other causes.

We do not understand the prejudice which still exists against the roentgen-ray in the diagnosis and management of pulmonary tuberculosis. Is it because some clinicians, who consider themselves expert diagnosticians, resent the fact that the roentgen-ray can give so much more information than their physical examination? For years medical literature has been full of facts as to the importance of the roentgen-ray, of which we will quote the following: McPhedran (6) states that there is no method that records the tuberculous invasion of the lungs and the progress or retrogression with accuracy approaching that of the roentgen-ray. He states further: "The x-ray is the method of precision for detecting the presence and evaluation of the exact severity and direction of the change of a lesion. The roentgenogram is the pivotal point of early diagnosis and the guide and index of effective treatment."

Webb (7) believes that the development of the X-ray in diagnosis and its use for the exact following of changes during treatment in tuberculosis is one of the most important developments of knowledge during the last quarter of a century.

We have tried to show so far in this paper that the old conception of activity is sadly wanting in efficiency; that constitutional symptoms are very unreliable, as they are often absent in active cases; that the grouping of criteria for diagnosis, as depicted by the Saranac Group and the

Veterans' Administration, although fairly reliable in advanced pulmonary tuberculosis, fails entirely in the diagnosis of certain types on account of the slight importance placed on the roentgen-ray.

It is only logical, therefore, that the old criteria must be modernized or discarded and new criteria adopted which will fit in with our newer concepts of activity; criteria, which if followed, will not fail in the diagnosis of all types of active tuberculosis.

The value of any conception or definition of activity in any disease may be said to depend on the accuracy with which it portrays the advance or subsidence of the pathological process (McPhedran (6)).

The old criteria fall far short of the above definition of activity. Râles, positive sputum, haemorrhage, pleurisy, constitutional symptoms, etc., are strong suggestive evidence of activity, but give us little information as to the advance or recession of the disease. The roentgen-ray, on the other hand, when properly used and interpreted, fits in perfectly with the above conception of activity.

At the present time, the trained clinician on reviewing a single set of films can in a large percentage of cases judge by the type of densities present whether the lesion is active or probably arrested. Have they (the densities) a soft cottony appearance with a fuzzy outline, or have they a hard appearance with sharply defined borders?

The clinician when in doubt as to the presence of activity has other means at his disposal. By the comparison of stereoroentgenograms taken at frequent intervals, he can view the changing pathological picture taking place in the lungs of his tuberculous patients with minute accuracy. In other words, activity may be considered in terms of anatomicopathological changes as portrayed directly before our eyes on the radiographic films. With this direct and exact method at our disposal, is it conceivable how some can still adhere to the old idea of symptomatic activity, the determination of activity by means of constitutional symptoms?

Activity once established we must not revert to the method, still in vogue by some, of setting a time limit to the continuance of activity, a relic of past ignorance developed before the roentgen-ray showed us our mistakes. We must continue logically, and consider a lesion active until by the comparison of roentgenograms we find that the densities have disappeared or have been replaced by stable and well-fibrosed lesions.

McPhedran (6) supports this view. He states: "The best evidence

of a healed lesion is to be found in the sharp dense strands which remain stable for months under competent roentgenographic control."

It is well to mention that some phthisiologists place a great deal of reliance on the sedimentation test and the monocyte-lymphocyte ratio as factors in determining the status of a tuberculous involvement. These are no doubt valuable aids in determining the stability of a lesion but should in no way displace the method outlined above.

It is not unusual to see cases with rather extensive cavitation to have normal sedimentation.[2]

CONCLUSIONS

1. The idea as to what constitutes activity in pulmonary tuberculosis has not kept pace with our other advances in knowledge.

2. Although the presence of constitutional symptoms may be considered a manifestation of activity, we must not conclude that the absence of constitutional symptoms means no activity. The old conception, therefore, that activity is determined by the presence of constitutional symptoms, should be discarded as very unreliable. The most exact method we have at our disposal is to consider activity in terms of the anatomicopathological changes which occur in the lungs.

3. In certain types of tuberculosis, of which childhood and the secondary (Ranke (2)) tuberculosis of adults are outstanding examples, the early diagnosis can only be made by the roentgen-ray, inasmuch as physical findings are usually absent and constitutional symptoms, if present, are so slight they are usually overlooked.

4. It follows that groups of signs and symptoms as diagnostic criteria for the diagnosis of active pulmonary tuberculosis, although a step in advance at the time, have greatly lost their usefulness; because by the methods outlined, it is impossible to diagnose the types of tuberculosis mentioned.

5. If such groups of criteria are to be used in the future, the roentgen-ray must receive the place of prominence in such a scheme. In short, positive roentgenograms unaccompanied by other criteria must be considered of sufficient evidence to diagnose active pulmonary tuberculosis.

[2] The method outlined for determining activity is feasible in the great majority of cases. It is realized, however, that the roentgen-ray is not infallible. In some cases in which densities are obscured by massive fibrosis or thickened pleura, or are concealed behind the heart, diaphragm or mediastinal enlargements, it is, of course, impossible to observe the progression or retrogression of the lesion in the radiographs as stated.

6. Comparison of serial radiographs taken at certain specified intervals should be considered the method of precision in determining activity in pulmonary tuberculosis. Cases should be deemed active as long as comparative radiographs show progression or retrogression[3] of the pathological lesion and arrested only after a lesion has remained stable for months under capable radiographic control.

Note: Some very helpful advice by Dr. E. A. Beaudet, our roentgenologist, is gratefully acknowledged.

REFERENCES

(1) RANKE: Deutsches Arch. f. klin. Med., 1920, cxix.
(2) REDEKER, F., AND WALTER, O.: Die Entstehung der Lungenschwindsucht des Erwachsenen, 1929, ed. 2.
(3) HEISE, F. H.: Râles in the prognosis of pulmonary tuberculosis, Amer. Rev. Tuberc., 1928, xvii, 327.
(4) HEISE, F. H., AND BROWN, L.: Study of occurrence of hemoptysis, pleurisy, râles, tubercle bacilli, and X-ray findings in 1000 consecutive cases admitted to Trudeau Sanatorium, Ibid., 1923, vi, 1078.
(5) Regulations and Procedure, Veterans' Administration, R. & P. Paragraphs 6020 and 6021.
(6) MCPHEDRAN, F.: Tuberculosis in childhood and adolescence, Tr. Nat. Tuberc. Ass., 1929, p. 125.
(7) WEBB, G. B.: Modification and developments of our knowledge of tuberculosis during the last quarter century, Ibid., 1929, p. 225.
(8) FISCHEL, K.: Nonapical infiltrations in pulmonary tuberculosis, Amer. Rev. Tuberc., 1931, xxiii, no. 2.

---

[3] Retrogression or clearing should be distinguished from the retraction of fibrosis. The former occurs when the lesion is soft, the latter when the lesion is hard after healing has taken place.

BOOKS[1]

ÉMILE SERGENT, FRANCIS BORDET AND HENRI DURAND, in technical coöperation with J. COUVREUX: *Exploration radiologique de l'appareil respiratoire. With 639 figures, including 580 radiographs, pp. ii + 463, 2 volumes, Paris, Masson & Cie, 1931, cloth. Fr. 350.*

By MAX PINNER

The important rôle that roentgenology plays in interpreting diseases of the chest need not be emphasized at this time, but this truly monumental French work is so impressive in a good many respects that even he who considers the roentgen-tube his daily tool will pause to reconsider its significance. The authors state in the preface that their atlas is an iconography and not a theoretical treatise, that it is based on personal observations over a period of more than ten years, and that the material is presented entirely from the clinical point of view. This latter emphasis does not preclude frequent references to pathologicoanatomical findings and comparisons of roentgenograms with anatomical specimens, this being admittedly the decisive confirmation of the reality and concrete actuality of roentgenological interpretations and appraisals.

In the first part of the work are discussed the technical essentials and the clinical value of roentgenological studies, while a second part is devoted to the

[1] The REVIEW plans to carry a section devoted to *Book Reviews* from time to time. It accordingly invites contributions of this nature from any authors who may see fit to submit manuscripts and will be glad to accept those reviews that measure up to standards that would comprehend such features as thorough familiarity with the text of the work under review, as well as knowledge of the subject and field covered by the book; apposite comparisons with related texts; critical ability and treatment; good literary form; and helpful description of contents. Uncritical praise and repetition of publisher's "blurbs" will be as undesirable as savage or personal attacks: neither will be tolerated. The main—almost the sole—purpose of an acceptable review should be to inform and to entertain. No limits or restrictions will be set on length of manuscript or manner of treatment provided the above-mentioned general considerations are adhered to. All reviews must be submitted gratuitously and those accepted will be published without compensation. Manuscript should be prepared in standard form (typewritten, one side of sheet only, double-spaced, etc.), and according to the style set in the reviews printed above.

Any opinions expressed are to be considered as those of the reviewer alone, and the widest latitude consistent with probity, ordinary courtesy and fairness will be allowed in this respect. In no way are they to be regarded as representing opinions of the publisher or editors.

In general, reviews will appear under the reviewer's name, initials or pseudonym. If, however, good and sufficient reasons can be adduced, worthy anonymous or unsigned reviews may be published, provided the author's name is known to the editor.—*Editor.*

study of "fundamental notions." This second part is probably the most interesting and valuable section. The authors create here what might well be called a "general roentgenology of the chest," in the same meaning that is familiar to all in speaking of "general pathology." This chapter is really a new departure in roentgenological literature, and its value lies in the clarity and the methodical guidance that it provides for a better understanding of the complexities presented by individual cases. It defines the terminology for objective description; it discusses fundamentally the significance of shadows according to size, shape, contour and density; it does the same for rarefactions. In a third, and by far the largest part of the book, are described "the radiological images in pathological conditions in the different parts of the respiratory system (thoracic cage, diaphragm, mediastinum, trachea and bronchi, pleurae and lungs)." To present an adequate review of this part would necessitate a recital of almost all anomalies and pathological conditions that occur in the respiratory system or secondarily affect it. The facing text is concise and admirable in its lucidity. The authors have used to full advantage the pictorial qualities of their language. The English-speaking reader may occasionally be somewhat confused by just this virtue of the presentation, because objective (frequently metaphorical) description fuses with actual terminology to give the impression of an unnecessary abundance of pathologicoclinical terms.

In the explanatory text that accompanies the roentgenograms special emphasis is frequently given to minor but revealing details, a most commendable method which (besides adding valuable diagnostic criteria) creates the impression that the reader is constantly in the hands of most thoughtful and experienced guides. The only criticism that the reviewer cannot suppress is the fact that in many instances the clinical data accompanying the roentgenograms are too scanty to furnish convincing evidence for the stated diagnosis. This is particularly evident in the section on pulmonary syphilis.

But any possible criticism is immediately silenced by the sheer beauty of the work. It is an admirable piece of bookmaking, in binding, in typography and, most of all, in the photographic reproductions which are of a high degree of excellence. The choice of the pictorial material is more than adequate for its stated purpose. Anyone interested in chest work will find in this work a veritable mine of information, most pleasingly and authoritatively presented. The American reader will detect many statements and opinions, particularly in the chapters on tuberculosis, that deviate from American teachings, but it is felt that this fact should represent an additional recommendation. It is a rare privilege to be able to recommend a medical book both for its scientific and scholarly qualities and for its artistic value.

R. NICOL AND G. SCHRÖDER: *Die Lungentuberkulose, Lehrbuch der diagnostischen Irrtümer. Second improved and enlarged edition with 160 figures and 2 tables,*

pp. iii + 328, München, Aerztliche Rundschau, Otto Gmelin, 1932, paper. R.M. 20.

By MAX PINNER

The art of diagnosis and differential diagnosis in pulmonary tuberculosis is undoubtedly one of the central problems in the tuberculosis campaign. The failure of achieving early diagnosis *en masse* is in large measure due to the pitfalls and errors in diagnostic work. Nicol and Schröder's book, admittedly a textbook and not a scientific treatise, is addressed essentially to the practitioner, and presents in concise and simple language the fundamentals of diagnosis.

Theoretical discussions of allergic phases, based on Ranke's work, are brief and restricted to the introductory chapter. In the second chapter, on pathogenesis, the terminology, the classification of developmental stages and the consideration of various modes of propagation of lesions, are considerably more complicated and elaborate (and at times more dogmatic) than necessities and facts seem to warrant. There is a lucid and eminently fair discussion of what has been known for some years in the German literature as the "old" and the "new" teaching of tuberculosis. By this is meant the antithesis between apical and subapical (clinical) incipiency, between insidious and sudden onset, between slow continuous and rapid discontinuous progression of lesions. In other words the "new" school emphasizes the clinical importance of acute allergic phenomena that were rather neglected by the "old" school, which overemphasized the chronicity of tuberculosis. The newer concepts eliminate a good deal of overdiagnosis by recognizing the frequent insignificance of slight physical signs at the apices. Early diagnosis, liberated from a considerable ballast of traditional and antiquated opinions, is then discussed in practical terms. Particular emphasis is given to the common sources of diagnostic errors in regard to physical signs, symptoms and roentgenology.

The next chapter presents some of the most common developments in pulmonary tuberculosis. This is done in the form of an atlas of well-selected and clearly reproduced roentgenograms and only brief explanatory notes. Another chapter is devoted to a discussion of the term "activity" and to "activity diagnosis." It is suggested that for practical clinical considerations, "active" should be used as a synonym of "in need of treatment" (*behandlungsbedürftig*). Activity cannot be diagnosed on the basis of single signs or symptoms, such as râles, sedimentation-test or blood-pictures; it is determined by observation of the patient as a totality, and it requires, in some border-line cases, a maximum of clinical judgment and experience.

About 90 pages are given to a discussion of differential diagnosis; the more important respiratory diseases are enumerated and the more or less specific points of differentiation from tuberculosis are stressed. Although some pathological conditions are ignored (for example spontaneous pneumothorax, Fried-

laender pneumonia, massive atelectasis) this chapter contains in adequate form what the practitioner should know about differential diagnosis. It is the reviewer's impression that this book fulfils the aim for which it was written; it is a safe and fairly conservative guide through the maze of diagnostic difficulties. It is very largely based on the wide experiences of its authors. It might, therefore, have been published without a list of references. But the list which is appended is objectionable because it is sketchy and incomplete without a discernible method of selection; and its linguistic narrowness (one French and two English references are given) is totally unwarranted. An index would have been helpful.

ALFONS WINKLER: *Die Perkussion der Lungenspitzen. With 66 figures in the text, pp. i + 135, Wien and Leipzig, Emil Haim & Company, 1932, paper. Mk. 6.00.*

By MAX PINNER

Following the work of Grancher, a new enthusiasm and new methods arose in diagnosing pulmonary tuberculosis in its incipient stages. For many years incipiency meant apical lesions. To diagnose apical processes, scores of physical methods were advocated and their overzealous application filled the sanatoria with clinically healthy individuals, and permitted many sanatoria to publish enviable records of cures. Since our concepts of clinical incipiency have changed materially during the last decade it excites some surprise to see the publication of a monograph devoted to percussion methods in apical diagnosis. Dr. Winkler discusses briefly the various methods and modifications that have been devised to diagnose real and apparent abnormalities of the pulmonary apices. Since his discussion is almost completely limited to technical procedures with only slight and rather vague references to clinical or pathological conditions, the reviewer fails to appreciate its usefulness in the present stage of tuberculosis work. Anyone, interested in a concise and critical discussion of all these percutory methods which have made courses on physical diagnosis more dull and complicated than necessary, will find in Dr. Winkler's treatise what appears to be an authoritative account.

R. NISSEN: *Über die neuere Entwicklung der chirurgischen Behandlung der Lungentuberkulose, with a foreword by F. Sauerbruch. With 3 figures in the text and 62 illustrations on 16 plates, pp. i + 16, Urban & Schwarzenberg, Berlin and Wien, 1932, paper.*

By MAX PINNER

Publications on the surgery of pulmonary tuberculosis have appeared in such numbers during the last decade that one is now inclined to inquire for a defi-

nite *raison d'être* for each new work on the subject. Professor Nissen's monograph has a definite purpose and fills a specific need: it summarizes in enviable brevity the experiences, results and methods in use in Sauerbruch's Clinic. Professor Sauerbruch is not only an outstanding pioneer in thoracic surgery, but, on account of sustained practical work, research and experimental investigations, and ably supported by a number of co-workers, he still is an unquestioned authority in the field. Professor Nissen's monograph, endorsed as it were, by a brief introduction by Professor Sauerbruch, achieves approximately what an interview concerning recent developments in the surgical Charité Clinic might have as its aim.

The text, occupying only 16 double-column pages, is concise, but not sketchy. Some of its most significant points follow in briefest summary. The procedure of choice for the artificial diminution of the lung and for its immobilization is artificial pneumothorax; larger surgical procedures are not justified without a previous attempt at pneumothorax. Whether the latter is possible or not can never be predicted; it must be tried. Endopleural pneumolysis remains indicated for the severing of single adhesions. The well-qualified surgical worker will frequently prefer open pneumolysis. In the presence of broad and numerous adhesions, thoracoplasty is preferable, because, in such cases, the cavity-walls are usually so stiff that pneumolysis remains inefficient. The method of choice for diaphragmatic paralysis is exairesis of the phrenic nerve. In connection with pneumothorax, exairesis is only indicated in the presence of basal adhesions. In this particular case the indications might be expected to be wider if the Sauerbruch Clinic would have more occasion to observe patients with pneumothorax to the completion of treatment. The value of Alexander's intercostal neurectomy and of scaleniotomy, with the complete removal of the first rib, is doubtful. Partial upper thoracoplasties are useful in incomplete pneumothorax. The upper eight ribs should be resected so that the scapula can fall into the costal defects. In the presence of apical cavities, this procedure should be preceded by an apicolysis, which then makes the total removal of the first two ribs unnecessary. Lower partial thoracoplasties are less efficient than phrenic evulsion. With but few strictly indicated exceptions, every thoracoplasty should be complete. The indications are again limited to productive or fibrous, and essentially unilateral, lesions. A final good result, depending so much on the compensatory function of the contralateral lung, can be expected only when contralateral pleural adhesions are absent. Neglect of this point is the cause of frequent disappointments. The major factors in failures are postoperative mediastinal flutter, circulatory failure and aspiration. The condition of the mediastinum should be tested by attempts at pneumothorax. The ability of the circulatory system to adapt itself to postoperative conditions is tested by having the patient breathe under increased and decreased air-pressure. Rapid decrease of blood-pressure and increase in pulse frequency

to 100 or 120 constitute warning signals. Patients below the age of 20 are more endangered on account of their soft mediastinal structures; patients above 40, on account of emphysematous changes. Thoracoplasty should not be done earlier than one to two years after the onset of the disease. In most patients, a two-stage operation is to be preferred. A one-stage operation may safely be performed on young patients in good general condition, and it may be indicated in the presence of large cavities in the midlung which would otherwise be exposed to disturbing movements between the operated and nonoperated part of the thorax. The lower stage is done first, allowing for the following exceptions: (1) if a free pleural space exists in the lower parts; (2) if a cavity is around the level of the sixth rib, so that it would be in the upper border of the operated area; and (3) if an upper stage may be sufficient. Three- or four-stage operations may be indicated by a questionable condition of the contralateral lung or by unsatisfactory circulatory function. Phrenicectomy should not routinely precede every thoracoplasty. With sufficient experience, local anaesthesia is best; but ether or gas need not be feared. Complete expectoration and atropin medication before operation safeguard against aspiration. Auxiliary operations may become necessary to increase pulmonary collapse: they are costal resection in the axillary line, which is more efficient than parasternal resection; apicolysis, combined with tamponing; localized extrapleural tamponing; and pneumothorax. Paraffine tampons (*Plombe*) are indicated in the case of localized, fibrous, cavernous lesions for which plastic operations cannot be done. A first prerequisite for this procedure is a thick, adherent pleura. Bilateral tamponing has not stood the test. A vital indication is presented in cases of massive haemorrhage and obliterated pleural space. The results of tamponing are best at the apices. The most dreaded complication is rupture of the tampon into the cavity. In patients in whom pneumothorax is impossible on account of an obliterated pleural space, in whom diaphragmatic paralysis has proved inefficient, and who could not stand a thoracoplasty, extrapleural pneumothorax following pneumolysis has been tried as a last-resort measure, with satisfactory results obtained in two out of five patients. An important addition to the text are 80 roentgenograms on 16 plates, and a few other illustrations. These are well chosen to illustrate and emphasize the discussion, and are exceedingly well reproduced.

P. REHFELDT, in collaboration with A. BACMEISTER: *Ernährung und Diät bei Tuberkulose. With 15 tables, pp. xi + 187, Dresden and Leipzig, Theodor Steinkopff, 1932, paper. Mk. 13.50.*

By MAX PINNER

The dietetic treatment of tuberculosis, once the hub of all tuberculosis therapy, has received relatively little attention in recent years, largely because of the

rapid development of surgical methods. With the exception of a few extremists, most phthisiotherapists are agreed that a rationally mixed diet, providing a sufficient number of calories and supplemented by vitamines, is the most desirable regimen for tuberculous patients. But, confronted with the task of selecting such a diet in detail, or to feed it to a patient with chronic anorexia, many a physician realizes the difficulties of the problem and becomes aware of the fact that diet, although divested of its previous sovereign importance, still requires the knowledge of a number of physiological and pathological facts, and a mastery of practical detail in that field in which the science of nutritional physiology and the culinary art meet. Rehfeldt's monograph attempts to provide each side of the problem.

In the first chapter the metabolism in tuberculosis is discussed. Although no specific alterations are known to exist in the metabolic processes in tuberculosis, changes do occur and should be adequately considered in establishing a dietary regimen. The known and some alleged facts concerning basal metabolism, the specific dynamic action, protein-, carbohydrate-, fat-, mineral- and water-metabolism are presented, and the conditions of the ionic balance and the rôle of vitamines are discussed.

The second chapter is devoted to "tuberculosis and constitution." The conviction that certain constitutional debilities may be corrected by a rationally planned diet is the justification for the inclusion of this chapter. The relation of certain constitutional types (based on Kretschmer's classification) to susceptibility and resistance assumes an ever-increasing significance in phthisiogenesis.

The third chapter enumerates, partly in tabular form, the more important foods according to their caloric and specific nutritional values. The rest of the book, approximately 100 pages, gives practical directions for nutritional therapy in tuberculosis in general and under specific conditions, such as in undernourished and in adipose patients, in patients with specific and nonspecific gastrointestinal impairment, in patients with diabetes and tuberculosis, and in patients with renal disease.

The whole monograph is unpretentious in form and in its claims. It does not attempt to exalt *one* method, nor to revolutionize the nutritional methods in common use; but it does direct attention to the fact, probably greatly overshadowed by the more spectacular phases of phthisiotherapy, that an adequate and individual adjustment of diet is still of fundamental importance. And it shows clearly and concisely the principles of nutritional therapy and their practical application. There can be no doubt that the knowledge of this book would improve greatly the food management in many places where tuberculosis patients are treated, particularly because Rehfeldt has taken great pains to show, not only principles and aims, but ways and byways by which the aims can be achieved even in the face of obvious individual difficulties. The book

can be warmly recommended to the physician treating tuberculous patients and particularly to dietitians in sanatoria. Its value would be considerably enhanced for the student and scholar by the addition of a bibliography.

INSTITUT PASTEUR: *Vaccination prêventive de la tuberculose de l'homme et des animaux par le BCG. Rapports et documents provenant des divers pays (la France exceptée) transmis a l'Institut Pasteur en 1932, pp. 366, Paris, Masson et Cie., 1932, paper.*

By MAX PINNER

Since it is now eight years that *BCG* has been used for the "vaccination" of human beings and cattle, a comprehensive report of these activities is most welcome. The present book contains 46 reports from 30 (not as stated 46) different countries and by various authors. In all these countries (with the exclusion of continental France) *BCG* has been used at some time during the last eight years, the number of reported "vaccinated" individuals per country varying from 293 (in Germany) to several hundred thousand in other regions. One who has followed the *BCG* literature encounters many names which have become familiar as enthusiastic proponents of this "vaccine," but one misses the method's opponents. Yet, it is obvious that, since this volume comprises only (with some exceptions to be mentioned) the practical application of *BCG*, the citation of opponents, who do not use the "vaccination," must be absent. However, the veterinarian literature does contain not a few unfavorable reports on the practical use of *BCG*, from authors who are not represented in the present collection. If, then, a first superficial glance reveals enthusiastic bias, this impression is deepened by further studies. Although some of the most obvious statistical errors in Calmette's earlier reports have been pointed out by unquestionable experts, no attempt to avoid them in this presentation or to correct earlier statements is discernible. It is now well established by a number of most careful reports that the mortality in the first year of life in tuberculous coresidence is somewhere around 7 per cent, but Calmette's figure of about 30 per cent still stands uncorrected.

The "vaccination" is done during the first 10 days of life, and only on healthy babies. This practice involves two major pitfalls for statistical presentation: (1) according to the statistics of various civilized countries, of all infants dying during the first year of life, about 14 per cent die during the first day of life, and from 14 to 29 per cent die during the first week; (2) the fact that only infants in good health are "vaccinated" removes from the vaccinated group some of the gravest liabilities and adds them automatically to the unvaccinated control group. In none of the reports are these sources of statistical errors accounted for. Some of the reports mention only the number of "vaccinated children," without adding anything about the results, or they add only a vague

general statement that the results were satisfactory. Relatively little information is given on morbidity, most statistics being based on mortality rates only. In most reports the mortality of the "vaccinated" infants is compared with the total infant mortality of the respective country. This is evidently an unpermissible comparison, because the nonvaccinated infants lack not only the "vaccination" of the *BCG* group, but the mothers do not receive the hygienic instruction and medical observation that go with it. More or less acceptable statistical elaboration is found only in some of the reports which comprise a statistically insignificant number of "vaccinated" infants. As a sort of summary, a table is presented on page 362 in which are reported 219,924 vaccinated children from 16 different countries: the total mortality of these children (birth to 1 year) is 6.36 per cent; the total mortality of nonvaccinated children in the same countries appears to be 17.0 per cent (not weighted average). The summary of this table in the text reads: "In a total of 443,656 vaccinated infants in 46 different countries, with the exception of France (according to the documents transmitted to the Pasteur Institute in 1932), the average general infant mortality from all causes from 0 to 1 year is: for the vaccinated ones 7.9 per cent, for the nonvaccinated ones 15.3 per cent, that is almost 50 per cent in favor of the vaccinated infants."

There is no reason to doubt that the Pasteur Institute received the reports on which this last statement is based, but it is disconcerting, and not in accord with the accepted practice in scientific work, to present only one-half of the evidence and to draw the essential conclusions from both halves. In the table referred to above, the infant mortality, without "vaccination," varies between 9.3 and 34.3 per cent. These mortality rates, which compare unfavorably with those of the United States, England and Central Europe, are reduced in average about 50 per cent, allegedly by the administration of *BCG*. It is significant to note that countries with high infant-mortality report the most striking reduction in the "vaccinated" group. Greece, for example, with a total infant mortality of 34.3 per cent, observed a mortality of only 7.3 per cent in "vaccinated" infants. It is obvious, however, that this reduction of some 78 per cent, or even the average reduction of nearly 50 per cent, cannot possibly be due to the prevention of tuberculosis, and hence cannot be credited to *BCG*. The part that tuberculosis plays in a total infant mortality is usally below 5 per cent: for example, 4.7 per cent in Vienna, and less than 2 per cent in Germany, Italy and England. The spectacular decline of the mortality in "vaccinated" infants as compared with the general infant mortality in the respective countries, is probably a fair index of the efficiency of general hygienic care and instruction, and its relation to *BCG* administration *per se* remains as obscure as ever.

Since about one million infants have received *BCG* without the occurrence of

ill effects, at least not in large degree, it may be assumed that *BCG* is probably harmless. Considering further the studies of Heimbeck in Oslo and of Park and his associates in New York on the parenteral administration of *BCG*, its innocuousness can hardly be attributed solely to a possible failure of absorption upon oral administration. Furthermore, the disaster at Lübeck has proved beyond doubt the ease with which orally-given tubercle bacilli pass the intestinal barrier. The last possible doubt of the harmlessness of *BCG* treatment will not be quieted until a sufficiently large number of "vaccinated" subjects have passed safely through puberty, during which period so many spontaneously infected human beings suffer exacerbations of previously latent infections. If innocuousness can then be granted for the present, and the present documents add considerable weight to this opinion, it should be emphasized again that the reviewer fails to see any convincing evidence presented in this volume for or against a protective action of *BCG*.

The first 47 pages of the volume at hand are occupied by seven papers by Professor Calmette and his coworkers, in which general and fundamental features relating to *BCG* are considered. Here are discussed the reports of those who believe they have observed a recrudescence of the virulence of *BCG*. Such results are explained as experimental errors, particularly emphasizing the probable interference of spontaneous infections in experimental animals. It is rather astonishing that neither side to this conflict of opinion has mentioned the obvious differences between spontaneous and inoculation tuberculosis. Park and his associates have repeated some of the experiments of other workers that produced virulent strains, but they obtained negative results. In spite of reiteration, the evidence for the experimental production of immunity in guinea pigs, rabbits and monkeys remains equivocal, and the good results reported from France on bovine immunization could not be repeated by a number of competent workers elsewhere.

It is regrettable that in spite of eight years of intensive work, a conclusive opinion as to the efficiency of *BCG* vaccination has not yet been reached. To arrive at one will likely require years of observation on treated human beings and on animals under rigid conditions of experiment; as, *vide* the several decades and the enormous experience necessary to appraise properly essentially similar attempts at protective inoculation of cattle and involving methods devised by the masters of tuberculosis —Koch and Behring—of a generation just passed. Meanwhile, one may restate that a continuing piling-up of contestable statistical data is not apt to hasten the settling of the problem.

KURT KLARE: *Die Prognose der offenen Lungen-Tuberkulose bei Kindern und Jugendlichen. With 6 illustrations and 15 tables, pp. i + 31, Stuttgart, Ferdinand Enke, 1931, paper. RM. 3.90.*

By MAX PINNER

The prognosis of tuberculosis in children is considered as practically hopeless by some authors; by others it is thought to be very good. In analyzing the various opinions it is at once evident that the discrepancies of contradictory statements is due to the fact that they are based on totally noncomparable clinical material. A report on a definite group of patients is therefore to be welcomed. Klare has analyzed the prognosis in a group of 377 children suffering from open pulmonary tuberculosis. They have all been for some time under the author's care in the sanatorium for tuberculous children in Scheidegg, Bavaria. The group comprised 279 girls and 98 boys, with ages varying between 2 and 17 years. The case-incidence showed a sharp rise at the prepuberty and puberty ages, particularly in girls. Of the 279 girls, 217 are in the age-group 10 to 14. The results are represented under three headings,—"dead," "under treatment" and "able to work." Forty-five children were under observation for from 10 to 15 years; their mortality was 95.5 per cent. A second group of 90 children, with an observation period of 6 to 8 years, had a mortality of 77.8 per cent, with 10 per cent under treatment and 12.2 per cent able to work. The third group comprised 152 children, who have been under observation from 4 to 6 years: their mortality was 63.1 per cent, while 27.0 per cent of them are still under treatment and 9.9 per cent are able to work. A final group of 90 children was observed for only 2 to 3 years; 38.9 per cent of these are dead, 50 per cent are under treatment, and 11.1 per cent are able to work. The differences in mortality are obviously due in large measure to the differences in the length of the observation period, but the statistics presented seem to indicate that the prognosis of open pulmonary tuberculosis in children has improved during the last 15 years. Based on a uniform observation period of 1 to 3 years for all four groups mentioned, the mortality declined from 69.0 per cent to 38.9 per cent. This apparent improvement is undoubtedly not unaffected by an abnormally high mortality in the war and immediate postwar period. However, early diagnosis and more frequent pneumothorax treatment in the later groups deserve consideration. Children from tuberculous families, approximately half of the total number, have a definitely worse prognosis than children from tuberculosis-free families. Children with "lymphatic constitution" tend more to chronic and benign disease. The conclusions which Klare draws from his studies are directed to conditions of local German significance. This study appears to be of definite value because the material is clearly arranged in such a fashion that the figures carry all that conviction that elaborate discussions so frequently fail to convey.

ERICH EBSTEIN: *Tuberkulose als Schicksal. Eine Sammlung pathographischer Skizzen von Calvin bis Klabund, 1509–1928, with an introduction by Georg B.*

Gruber. With 8 portraits, pp. vii + 184, Stuttgart, Ferdinand Enke, 1932, paper. RM. 6.50.

By MAX PINNER

Many attempts have been made to clarify the influence that tuberculosis exerts upon the mental and emotional life of its sufferers. The fact that so many people, prominent in various walks of life, have had the disease has given rise to fanciful and attractive speculations at to the stimulating action of tubercle bacilli on the higher functions, although the number of prominent victims of the disease proves apparently nothing beyond the impartiality of the "white plague" in selecting its victims. And since tuberculosis does not respect any class or type of human beings we must of necessity expect to see a most variegated group of men and women living under the shadow of tuberculosis. Even without some mysteriously specific "toxin" to influence and shape human character and achievement it is evident that, by limiting certain activities, by shortening life, by being a *memento mori*, by causing pain, discomfort and fatigue, tuberculosis is and has been a great modifier of human life, whether by depressing and limiting body and mind, whether by the rebound that it may evoke in so many patients.

Some such considerations must have been in Ebstein's mind when he, well-known medical historian and *causeur*, set out to assemble the biographical data which are now published in a posthumous collection. These are presented as sketches, nothing more; and the reader must do more than his usual share of reading between the lines to extract the meaning and significance out of the bare and naked facts set down. The clinical histories are told briefly, but we miss (with the title's promise in mind) the connection between the disease and the life in most instances. Chronologically the collection embraces more than four centuries, starting with stern and unrelenting John Calvin and ending with the recent German poet Klabund, who wove frivolity and sentiment into a tissue of scintillating charm. Here is presented the painter (Watteau); poets abound (Goethe, Schiller, Annette von Droste-Hülshoff, Keats, Jens Peter Jacobson, Gorki, Chekhov); there are musicians (Weber, Chopin, Paganini); scientists (Laennec, Paul Ehrlich, Albrecht von Graefe, Wilhelm Wundt); actors (Iffland, Eleanora Duse and Corona Schroeter whose immortality is assured by her friendship with Goethe); sovereigns and statesmen (Louis XIII, and, behold the impartiality, August Bebel); philosophers (Spinoza); pedagogues (Pestalozzi). Some fifty sketches are assembled.

In his introduction Gruber succeeds in giving meaning and purpose to the data that follow by discussing some general principles of reactions toward disease. He makes an interesting attempt to correlate Kretschmer's physical and psychological types with the individual's resistance to the ravages of infection. The still unwritten book deserving of the present title will undoubtedly

profit from Ebstein's compilation. As it stands, with all the earmarks of an unfinished work, it bears witness to the untold variety with which human nature copes with (submits to or conquers) disease: *vide* the "philosophical," used here in the meaning of an honest attempt at profound thinking, and not in its degenerate meaning of "patient"; the religiously resigned; the rebellious; the terrified; the fighter who on the rebound intensifies activity and achievement.

Some of the human documents quoted in this book are of deep interest. Klabund says, "A history of literature of the tuberculous ought to be written. This constitutional disease has the property of altering the souls of its victims. They bear the mark of Cain—of intraverted passion which eats lung and heart." Or, writing of Christian Morgenstern, that whimsical poet and philosopher: "One can 'suffer' from anything, but in order to be 'ill' one must be possessed by an alien something; one must have become the slave of one's disease." And Börne writes: "Sick people say: 'Health is the greatest treasure.' But sick people have not a sound judgment. One might as well say, 'Life is the greatest happiness,' while it is after all only a condition to happiness." These few passages are quoted merely to show the justification for (and the fascination of) the book that Ebstein was prevented from completing.

RECENT DEVELOPMENTS IN OUR KNOWLEDGE OF TUBERCULOSIS[1,2,3]

J. ARTHUR MYERS

The Mississippi river is crossed by three persons; one near Lake Itasca, one near the Gulf of Mexico, and one at the midway point. No one sees any more of the river than the place of crossing, and, if each then writes a description, not one of the descriptions, nor the three combined, will give a clear conception of the river. If another person plied the river from its source to its mouth, observing it longitudinally and then wrote an account, the result would be a comprehensive description. In the study of structure of human organs or parts of organs cross-section observations made at different levels may give one a misleading conception, but if one makes cross-sections serially of the entire part to be studied and magnifies each one, makes drawings, and reconstructs the part in wax or blotting paper, a true description of the organ may be prepared. Forty-five years ago, when William Snow Miller began his studies on lung structure, only cross-section knowledge was available. Through his ingenuity in reconstructing lung tissue we have come to know the finer anatomy of the lung. To-day, wherever lung structure is studied and taught, Miller's contributions constitute the basis. This work has been so fundamental, so accurately done, and so far-reaching, that as long as medicine is practised the work of William Snow Miller will affect it profoundly.

I can imagine no finer act on the part of the Alpha Pi Chapter of Phi Beta Pi Fraternity than your attempt to perpetuate the splendid research spirit which has lived so long in the laboratories of Doctor Miller. If I am permitted to make a suggestion, it is that the members of your active chapter, together with your alumni members, put forth every effort to stimulate, encourage, and support Doctor Miller in the preparation of a monograph in which he will bring together his vast store of

[1] The William Snow Miller Lecture, presented at Madison, Wisconsin, March 31, 1932.

[2] From the Departments of Preventive Medicine and Internal Medicine, University of Minnesota, and the Lymanhurst School for Tuberculous Children, Minneapolis, Minnesota.

[3] Prepared with the aid of a grant from the Medical Research Fund of the University of Minnesota.

information. The entire field of medicine needs such a monograph; the anatomists are eagerly anticipating it. Only with adequate knowledge of the normal chest can the pathology of the disease in the chest be comprehended. The lack of such knowledge on the part of the early workers made the history of tuberculosis what it was,—mainly a matter of guess-work.

In the history of tuberculosis, we find only a few well-established facts, although volumes have been written from opinions. In the beginning of our historical records, physicians were almost entirely dependent upon the senses unaided. It is true that they made some keen observations, but they did not have the facilities for establishing scientific facts. They could see the patient wasting away and finally dying; they could hear sounds from within the chest when placing the ear directly against the chest-wall; they could see person after person dying from this disease in the same family; they could think and reason; they could speculate as to the cause of death; but their reasoning was not always good because they had almost nothing definitely established from which to begin. The speculations of one group concerning the heredity of consumption were just as good as those of another group concerning its communicability.

Observation at the postmortem table established certain facts, such as the prevalence of tuberculosis and ability of the human body to control it, but under just what conditions it was brought under control no one knew. Just why there appeared a tendency for one group of lesions to come under control and another to progress; why lime was found in one group and fibrous tissue in another; why cavitation appeared in one group frequently and in another group rarely; why miliary tuberculosis appeared in one group and not in another, no one knew, and yet there was much speculation. Venturing of opinions stimulated thought; thought led to methods of establishing certain facts.

The first fact of significance concerning the cause of tuberculosis was established by Klencke in about 1843, when by inoculation he transmitted tuberculosis from man to animals. His experiments proved that there is something in the material expectorated from the human tuberculous lung, or collected from it at postmortem, which causes the disease. A classical work on the transmissibility of tuberculosis was published by Villemin in 1868. The cause of the disease discovered by Koch was the next fact to be established. The demonstration of the tubercle bacillus as the cause of tuberculosis gave the enemy of tubercu-

losis a vantage point from which to clearly visualize tuberculosis. The communicability was thus incontrovertibly established. After the discovery of the bacillus, Koch developed tuberculin from the bacillus which he thought would cure and prevent tuberculosis. Although tuberculin did not prove to have the curative or preventive qualities which he had anticipated, it has become our most specific diagnostic agent.

Different methods of the administration of tuberculin include, among others, the subcutaneous of Koch, the unabraded skin of Moro, the abraded skin of Pirquet, the intracutaneous of Mantoux. Careful observations of the tuberculin reaction by all these different methods have been made, with the result that we now know about the advantages and disadvantages of the different measures. The subcutaneous administration is not always safe; the Moro and Pirquet methods with their modification are reasonably accurate, but the Mantoux method is the most accurate tuberculin test and at the same time is harmless.

Tuberculin may be introduced into the bodies of people and animals in large amounts without any reaction or any harm, provided tubercle bacilli have not produced a first infection in the body. On the other hand, a minute amount of tuberculin results in a reaction of the tissues, manifested by oedema and hyperaemia at and about the site of its administration, if tubercle bacilli have found lodgment in the body and have resulted in disease, even though this be microscopic. Persons who have been so infected with tubercle bacilli are therefore allergic or hypersensitive to tuberculin, just as some persons are hypersensitive to ragweed pollen. The tuberculin test, therefore, informs us with accuracy who, in a family or a community, has been infected with tubercle bacilli.

The pioneers in tuberculin-testing usually applied the test in tuberculosis clinics, to the children of tuberculous patients, or in cities where tuberculosis was extremely prevalent. The result was that large numbers reacted positively, and the opinion grew that tuberculous infection is universal in the human family by the time early adult life is reached. No one had applied the test to large numbers of persons in various parts of the world; nevertheless, the omnipresence of the tubercle bacilli and the impossibility for human beings to go through life without exposure to them was generally accepted. This led to the popular belief of to-day that everyone has, or has had, a "touch" of tuberculosis.

Indeed, since it was accepted that all young adults have been infected with tubercle bacilli, attempts were made to justify a condition over

which man had apparently no control by stating that tuberculous infection is an advantage. What was the truth when the tuberculin test was actually applied to large numbers of persons living under different conditions? It was very different from what we had been taught. Yet the earlier teachings may have been true then, although there is no proof.

In other words, great changes in conditions have occurred. An attack had been made on tuberculosis among animals, as well as human beings, and the opportunities for tubercle bacilli to reach the human body had been very definitely reduced. Perhaps there was a time when so much of the milk and other foods taken by children was contaminated by tubercle bacilli; when so many open cases of tuberculosis existed in many communities that few or no children grew to adult life in such communities without having been infected with tubercle bacilli and becoming hypersensitive to tuberculin. One may liken such a situation to a wooded country. Before such a country is inhabited, the uniform density of the forest is broken only by rivers and lakes, but in order to produce the necessary foods the settlers clear trees from areas of land. In time, such cleared areas are numerous and result in an entirely different appearance of the country. Finally, it is only here and there that one finds a sizable forest. For the most part, only wood lots remain. As the population increases and more cleared land is necessary for the production of food for man and animals, even the wood lots disappear and eventually there are huge areas of land without trees, or with a tree here and there.

In America perhaps tuberculosis was not as uniformly distributed among people and animals as the trees of wooded country, and in all probability areas remained free from tubercle bacilli, which might be likened to the rivers and lakes of a wooded country. At any rate, we have good evidence to lead us to such a belief from our recent tuberculin testing of man and animals. When the tuberculosis campaign began, the workers like the woodsmen began to direct their efforts toward eradication of this disease. In some places the intensity of the work was greater than in others, and the disease began to disappear faster in such places. If we could at present apply the tuberculin test to all human beings and their domestic animals in America, we would probably find some areas which may still be likened to forests, where the incidence of positive reactors to tuberculin is as great as it was two or three decades ago. We would find other areas where tuberculosis has become a rare disease. Such areas might be likened to the cleared land with only an

occasional tree. These would be the two extremes, and between them we would find great areas where much had been accomplished toward tuberculosis eradication but heavily infected areas comparable to the wood lots would still remain. We have good reason to believe that, if the campaign is permitted to continue and is intensified, we can now rather rapidly remove the isolated foci as we would remove the occasional tree on the cleared land. We can destroy the heavily infected areas or nests of tuberculosis and eventually use all of our forces in attacking the disease in those large centres which are veritable forests. Through tuberculin testing, X-ray examinations, postmortem findings, etc., man has learned of some of the strongholds of tuberculosis, such, for example, as those existing among the cattle and other domestic animals, the Indians, the Negroes, and the nursing and medical professions. Rather recently, definite campaigns have begun to drive tuberculosis from these strongholds. The medical asepsis, as practised in the Charles V. Chapin Hospital, Providence, Rhode Island, the Ancker Hospital, St. Paul, Minnesota, and the Fairview Hospital, Minneapolis, Minnesota, are outstanding examples of the nursing phase of the campaign. Worthwhile work has already been done in eradicating tuberculosis from domestic animals.

Some of the evidence which forms the basis of the above distribution of the incidence of tuberculosis is found in recent studies of the incidence of positive tuberculin reactions. Broker, of the Battle Lake Sanatorium in Minnesota, reports a township in which examination of 160 girls and boys in a school disclosed only one child who reacted positively to the tuberculin test. When the cattle of that township were tuberculin tested, not one positive reactor was found. Cotton, of the Live Stock Sanitary Board of the State of Minnesota, has recently reported a county in which, on the first tuberculin testing of the cattle, no positive reactors were found. McCain has called attention to an area in North Carolina where only approximately 4 per cent of all persons tested reacted positively to the tuberculin test.

From this we go to the opposite extreme and find Hetherington and others of Philadelphia reporting 90.2 per cent positive reactors among young adults by the time they reach the age of eighteen years. This figure is not much different from the figures of the early workers in Europe, such as Pirquet, and Hamburger and Monti. However, one must not conclude that in all parts of Philadelphia such a high incidence of positive reactors exists. The work of Chadwick and Zacks has proved

that, in a city where the tuberculin test is carefully and extensively applied, there will be found areas heavily infected in contrast to those lightly infected. They found that in one section of a Massachusetts city 60 per cent of the children reacted positively to tuberculin, while in another section of the same city only 11 per cent gave such reactions.

Between the low extreme found by Broker, Cotton, and McCain, and the high extreme found by Hetherington, have been reported varying incidences of positive reactors. Rathbun finds 25 per cent of children in smaller towns and 41 per cent of children in the largest cities in Chautauqua County, New York, reacting positively to the tuberculin test. Slater in southwestern Minnesota found only approximately 10 per cent of the school children with positive tuberculin reactions.

Among college and university students some very interesting data have accrued. At the University of Minnesota, where tuberculin tests have been administered to the entering freshmen since 1928, only approximately 33 per cent have been found to react positively. At the University of Pennsylvania this year, 1931–1932, 49 per cent of the entering students reacted positively to this test. At the University of Wisconsin in the fall of 1931 only approximately 30 per cent of those students tested reacted positively. Thus, one might go on with numerous reports from different parts of the country, but one would be compelled to conclude that the incidence of positive tuberculin reactors among human beings and domestic animals depends upon the opportunities they have had for exposure to tuberculosis. One of the most encouraging developments is the interest being manifested in tuberculosis control by those in charge of children in our public-school systems. Members of boards of education, superintendents of schools, principals, teachers, and parent-teacher associations are in some parts of the country coöperating closely with the nursing, medical, and public-health professions. A striking example of this will be seen in the program of the annual meeting of the California Tuberculosis Association to be held in Oakland, April 18 and 19, where school authorities are actually presenting papers before the section on childhood tuberculosis and the schools.

The slogan of the spring education campaign of the National Tuberculosis Association for 1932 is, "Tuberculosis Causes Tuberculosis—Every Case Comes From Another." This tells the whole story, namely, that tuberculosis is a communicable disease. The recognition of this fact has done more to change conditions with respect to the incidence of

tuberculosis than all of the steps that have been taken toward the control of this disease. The unfortunate fact remains that, although we have known the disease to be communicable, we have not always used this knowledge in the expenditure of funds and in the dissemination of publicity intended for tuberculosis control. That the 1932 slogan will result in an awakening of a public consciousness of the communicability of this disease is much to be desired.

Within the past few weeks I have seen an ambulance driver with large numbers of tubercle bacilli in his sputum; an orderly from the same hospital with extensive but previously undetected tuberculosis; a maid from a hospital, whose assignment was to kitchen duty; a laundress, working in the hospital laundry; and more than one nurse and more than one member of the medical staff of the same hospital suffering from previously unsuspected tuberculosis. What are the chances of the child, who has never been exposed to tubercle bacilli, but who falls ill from some other disease, and is taken to the hospital in the ambulance, receives services from the orderly, eats food handled by the maid, wears bed clothes handled by the laundress, is given intimate care by the nurse, and is visited by the medical staff-man, all of whom have tuberculosis? Although this is an actual experience, I admit that it is an extreme case. Yet if sufficiently careful examination were made, tuberculosis would be found in a communicable form in the employees of many of our hospitals. What is the result of allowing unsuspected cases of tuberculosis, in almost every walk of life, as found among trainmen, post-office employees, teachers, clergyman, grocerymen, waitresses, dairymen, etc.? In the wake of these individuals there follows a group of girls and boys and adults who have been made hypersensitive to tuberculin because they have developed at least the first-infection type of tuberculosis and, therefore, react positively to the tuberculin test.

How do these infected individuals tolerate tubercle bacilli and what is their future? Contrary to teachings of the past, the infant tolerates first infection very well, indeed. The finding of a parenchymal lesion in the chest of a child of two years or under, or the finding of a positive tuberculin reaction, no longer justifies a grave prognosis. There is abundant evidence which proves that the infant usually does not succumb, nor does he necessarily become ill from the first-infection type of tuberculosis. If he develops a parenchymal lesion which is demonstrable, it usually comes under control in from a few months to a year or so, and may leave nothing demonstrable by examination to indicate its

former presence except calcium deposits in the parenchyma and in the regional lymph nodes.

If the first infection with tubercle bacilli is postponed until the period of childhood, the reaction appears to be very much the same as in the infant. It may cause temporary illness manifested by mild symptoms. There may even be an allergic reaction, such as the development of pleurisy with effusion. Ultimately, the parenchymal shadows disappear, and, if any evidence remains which can be demonstrated during the lifetime of an individual, it is in the form of lime deposited at the former site of the infiltration and in the region of the lung hilum.

When the first infection with tubercle bacilli is postponed until young adult life, that is the teens or twenties, our observations have shown that the reaction is approximately the same as in those cases in infancy or childhood. We have been able to observe students in schools of nursing and medicine, negative to the tuberculin test, who after exposure in their training became positive to the tuberculin test and later presented tuberculous lesions which are reacting precisely as such lesions do in infancy and childhood. Therefore, if we postpone tuberculous infection until young adult life the infection does not cause galloping consumption, as was formerly taught.

In addition to our own work, we have as evidence that of Heimbeck and Geer. Heimbeck's work was done in the Ulleval Hospital with a bed capacity of 1,500, approximately 300 of which are tuberculous patients. These patients are for the most part advanced cases of pulmonary tuberculosis. Somewhat to Heimbeck's surprise, he found that only approximately 50 per cent of the probationers in the school of nursing reacted positively to the tuberculin test, but by the time they were ready to graduate 100 per cent reacted positively. Therefore, those who were negative on admission became positive while in training and apparently received their infection from the tuberculosis services. Tuberculosis morbidity of nurses in training was then observed, and Heimbeck found that, among the probationers of 1924, seventeen of the fifty-one who started with negative tuberculin reactions eventually contracted the disease, while only one of the fifty-eight starting with positive reactions developed tuberculosis. In the class of 1925 there were seventy-two giving negative reactions, twenty-one of whom developed tuberculosis during their training, while among forty-two giving positive reactions only one developed tuberculosis. In the class of 1926, sixty-two reacted negatively to tuberculin but during their training fifteen of them

developed tuberculosis. Fifty-two members of this class were positive to tuberculin on admission to the school and only one of them developed tuberculosis. By the time he prepared the manuscript of the article which appeared in June, 1931, eighty-one student nurses had developed evidence of tuberculosis. Seventy-one of them were among those who were negative to tuberculin as probationers and ten among those positive to the tuberculin test as probationers. The interval between exposure and the development of evidence of disease was not great. In fact, he found that, during the first six months after training began, there were 36 cases; during the second six months, 16 cases; and during the whole of the second year 18 cases, while after the second year there were only 6 cases. He concluded, therefore, that there is not a long latent period between exposure to tuberculosis and the outbreak of the disease. The question which immediately arises is, did these student nurses, previously negative to the tuberculin test, develop the first-infection type of tuberculosis? Heimbeck lists all of his cases as follows:

Pulmonary infiltration (21 cases: 7 with, and 14 without demonstrated tubercle bacilli).
Erythema nodosum, pulmonary infiltration (16 cases: 1 with, and 15 without demonstrated tubercle bacilli).
Erythema nodosum, pleurisy (4 cases).
Erythema nodosum, pleurisy and peritonitis (1 case).
Erythema nodosum (16 cases).
Pleurisy (15 cases).
Pleurisy, pulmonary infiltration (6 cases).
Pleurisy, coxitis (1 case).
Caries of the ribs, pulmonary infiltration (1 case).

One immediately becomes interested in the location, appearance, duration, etc., of those listed as pulmonary infiltrations. In a personal communication of December 21, 1929, Dr. Heimbeck makes the following very enlightening statement:

The general location is infiltration close to the hilus and enlargement of the hilus glands. In some cases the infiltration has on the Röntgen picture the form and location, which the Germans call "Frühinfiltrat," and which I am consequently absolutely sure of is the prime infiltration and immediate result of the prime infection (of the Pirquet negative, earlier uninfected).

If these infiltrations are diagnosed very early, before anything wrong is heard, that is: only on the bases of the tuberculin test, the general symptoms

of a Febris catarrhalis and the Röntgen investigation, the prognosis is benign, which you will understand when I tell you that of my 79 cases of TB among nurses, only 3 have died. And the greatest part of them have, after about one year's treatment, been quite all right and able to take up their nurse job again.

It is of great significance to note that the lesions in the negative tuberculin reactors were of the first-infection type and that in most of the 79 cases the prognosis was good. It appears, therefore, that these students of nursing, previously negative to tuberculin, develop their infection and react to it as children.

Geer, working in the Ancker Hospital with a bed capacity of 975, 215 of which are devoted to tuberculosis, found that only 30 per cent of the nurses entering the training school were positive to the tuberculin test, whereas practically all became positive after having taken a tuberculosis service. In five other general hospitals without tuberculosis services, only 42 per cent of the girls in the senior year reacted positively to the test. Among 110 nurses in training at the Ancker Hospital, six (or 5.5 per cent) developed tuberculous disease which could be located by examination. Five of them were negative to tuberculin on admission to the school and one was positive; three had pleurisy with effusion; two pulmonary disease, which he believes to be of the adult type; and another with a lower-lobe lesion, which he believes to be of the childhood type.

In Denmark the morbidity from tuberculosis among student nurses with positive tuberculin reactions on admission was 4 per cent, while among those with negative tuberculin reactions on admission it was much higher. Here again we have an example of the transmission of tuberculosis from patients to uninfected student nurses, which produced in their bodies the first-infection type of tuberculosis.

There is not a long latent period between exposure and the development of the first-infection type of tuberculosis, either in children or adults, but a very long interval of time may follow exposure and adult type of disease. Therefore, when one considers the insidiousness with which the adult type of pulmonary tuberculosis develops, one is not surprised that so few of the students of nursing in the groups of Heimbeck and Geer, who reacted positively to tuberculin as probationers, showed manifestations of disease. The following case illustrates this point:

In 1927 a university student reported for an examination because her room-mate had definite pulmonary tuberculosis with tubercle bacilli in the sputum. The contact had been intimate and somewhat prolonged.

At that time the entire examination was negative although, much to my regret, the tuberculin test was not applied, nor had she ever been so tested. In March, 1931, she was again examined, and this time the X-ray film showed evidence of Ghon tubercle-formation in the right upper lobe. In March, 1932, she had frank pulmonary tuberculosis, with cavity-formation involving the right upper lobe.

Another significant fact about the cases of Geer and Heimbeck is that the student nurses were being very carefully observed for tuberculosis. Lesions were revealed which in times past would in all probability not have been detected. In other words not all of these students would have been considered clinical cases in the early days of tuberculosis work. Perhaps most of those with allergic reactions, with such manifestations as pleural effusions, would have been, but in many of the others the lesions might have appeared without arousing the attention of the patient, and would have come under control just as those which have been observed in the chests of infants and children.

Many workers have reported on whole families of children, who react positively to the tuberculin test and whose chests show evidence of the childhood type of tuberculosis in its various stages of development; some in the inflammatory stage with a good deal of collateral inflammation and others with calcium already deposited. Upon taking a history, one finds that perhaps one, or, in many families, none of the children has been ill. Yet one attributes the evidence of the disease to the exposure of the children to the tuberculous member of the family. Now we simply trace infection by the tuberculin test and locate the lesions when they are sufficiently large to be found by our present methods of examination in young adults, just as we do with children.

Inasmuch as postponement to adult life of the first-infection type of tuberculosis does not result in galloping consumption, we are forced to ask what advantage a first-infection type, resulting in positive tuberculin reaction, is to the human body. We have always believed that it protects, but against what does it protect? As it occurs in ordinary human experience, we believe that the first-infection type of tuberculosis kills but rarely, or not at all. If one introduces huge numbers of tubercle bacilli into the body with a hypodermic syringe, as we do in the case of laboratory animals, or, as may have occurred in the Lübeck disaster, it is very easy to kill with a single dose, but, when tubercle bacilli are first taken by the respiratory or the digestive tract, it seems that they are usually well tolerated.

If disaster comes, it occurs for the most part in the bodies of persons who have already developed the first-infection type of tuberculosis and is usually remote in point of time. The infant who dies at the age of six months from generalized tuberculosis, probably had its first-infection type appear several months before, thus resulting in allergy or hypersensitiveness to tuberculin. If an infant with a positive reaction continues to receive large doses of tubercle bacilli from a tuberculous parent, or has a rupture of a caseous lesion in a lymph node, the tubercle bacilli will find lodgment in allergic tissue and, if they are sufficiently numerous, particularly when spread haematogenously, the body is overwhelmed. If this does not occur during the period of infancy, it may occur at any subsequent time in life. I have recently seen a patient of fifty-eight years die of miliary tuberculosis, who carried Ghon tubercle and large calcium deposits in the regional lymph nodes. Her eighty-year-old father had positive sputum.

If one studies mortality curves, one sees that infancy is a destructive period. We believe this is due in part to the huge doses of tubercle bacilli transmitted to the helpless infant. In other words, we believe that there are large numbers of infants who survive tuberculous infection and that it is only those who receive large doses of bacilli, after developing the first infection, who succumb to the disease. We have good reason to believe that even many who receive large doses survive. We have no scientific evidence to prove that the infant is more susceptible than the adult, yet its little body may not be able to tolerate the same doses as an adult. Krause proved this very conclusively in animals. The mortality curves also show that as the child's opportunities of exposure to large doses, through kissing, etc. decline, the death-rate decreases very materially and remains low until the time of puberty and the following decade or more. Going almost hand in hand with the appearance and the yearly increasing prevalence of venereal disease comes the sharp increase in the tuberculosis mortality curve. Here the possibilities of the transmission of huge doses of tubercle bacilli from the girl and the boy suffering from tuberculosis are obvious. I have seen one young man whom I believe to be responsible for serious tuberculosis in the lungs of two teen-age girls whose X-ray films showed no evidence of that disease prior to their association with him. But when tuberculosis strikes in a destructive form during and after the period of puberty, there has been some preparation of the soil. This preparation, we believe, is the hypersensitiveness or allergy resulting from previous first

infection. Krause's explanation is the most logical that has ever been presented. He says:

> Accordingly, the allergic reaction is seen to be responsible for all the acute manifestations of tuberculosis, and when so considered it must be viewed as a potent contributor to pathogenesis. Human beings pass as perfectly well as long as they hold their tuberculous infections asymptomatic, inactive. But they are allergic; and any discharge of sufficient focal material to a new place will render them immediately ill because of the allergic reaction that ensues promptly.

We may theorize a great deal, but ultimately we must come back to tuberculosis as it actually attacks the human body. Not one of us can escape the fact the great destruction from tuberculosis occurs in adult life. When careful histories are taken of persons suffering from clinical, destructive tuberculosis, the number who know of having been exposed at some remote time in the past is large. When we actually investigate sources of those who know of no previous exposure, we are astounded at the frequency with which we uncover unsuspected sources among the relatives and close associates, all of which increases our belief that the first-infection type of tuberculosis usually precedes by months or years the destructive type.

Further excellent evidence is obtained from the postmortem table. The fact that Opie found deposits of calcium in the chests of 98 per cent of white persons with the destructive type of tuberculosis cannot be ignored. The fact that Rich and McCordock, in the vast majority of their cases, found solitary tubercles, etc., in the central nervous system, which ruptured so as to transmit an abundance of tubercle bacilli to the subarachnoid space before meningitis developed, is good evidence that even tuberculous meningitis does not result from first infection directly, as we once believed, but that it develops upon allergic soil, made so by previous infection. Krause says: "A patient falls ill with tuberculous meningitis, and dies. At autopsy we observe little that is wrong or significant, except a stippling of minute tubercles at the base of the brain, and, if we are lucky, an old solitary fibrocaseocalcareous tubercle, the parent focus, in a lung or the tracheo-bronchial lymph nodes."

Thus one sees that the body reacts almost as differently to the first infection type of tuberculosis and to the reinfection type as it would to two different diseases. Stewart says: "Our ideas about children lagged a generation behind our knowledge about adults, chiefly because we had a

single standard for measuring alike disease in the adult and child. But the two types are almost two diseases, so different that they have little more than the causal organism in common." This statement applies, in our opinion, whether the first-infection type of disease develops in infancy or senility, or at any intermediate time, or whether the adult type of disease develops in infancy or adult life. Recent studies on the first-infection type of tuberculosis in the bodies of the same children over periods of years have almost completely revolutionized our views concerning certain phases of tuberculosis. Stewart has admirably expressed this fact as follows:

> The discovery of the child in tuberculosis opens up a great new continent for exploration. It is in this new continent of childhood that the most fruitful explorations of the anti-tuberculosis forces will be made during the next generation. These sunrise people of a new day are always new, always fresh, always invite our quests, always more than repay what we can do for them. What we wish to do for the race must be done for the child. On their behalf we must even learn a good part of our tuberculosis all over again.

Now that we have been compelled to learn a good part of our tuberculosis over again, we are visualizing its control as never before. Optimism is being expressed everywhere by those who have carefully followed the recent developments in our knowledge of tuberculosis. The following practical applications of the recent developments give us an idea of what is possible and justify much optimism:

Dr. Hilleboe became curious about the tuberculosis status of 60 children four years old and under, who were enrolled in a nursery school. He applied the intracutaneous tuberculin test and found that four of them were positive reactors. Since every case comes from another, he began searching among their associates. An early revelation was that two of the teachers had tuberculosis, one definitely of the adult type. Members of the families of these children are now being studied for tuberculosis. Finding the source and ending the exposure is the best treatment for the children. Treatment of the patients who infected the children may begin much earlier than it would have without such an investigation, and such treatment should be the means of saving large numbers of other persons from unsuspected exposure.

Simons and Hilleboe applied tuberculin tests and X-ray examinations in a case-finding endeavor in a small rural community with the result that 19 new cases of tuberculosis were discovered. When they enlisted the support of the veterinarians 18 cows supplying milk to the community

were found to be infected. Gibbons has done similar work in another rural community. If their work is continued, and tuberculin-testing is more generally applied to the children of the community at six- to twelve-month intervals, the time will be near at hand when the advanced case of tuberculosis will no longer be found in the community and when tuberculosis in any stage will be a rare disease.

There have been two stumbling-blocks in our present program of tuberculin-testing and X-ray examinations of positive reactors as a case-finding measure. The first is the objection presented by parents and others to instrumentation in the administration of tuberculin. In the hands of most workers the Moro test has not proved as accurate as the Pirquet test. However, Lovett has called attention to the percutaneous test, which consists of rubbing the skin with ether until hyperaemia appears, in an attempt to remove the oil from the pores. Then a preparation containing tuberculin is rubbed into this area of skin. She finds this test fully as accurate as the Pirquet test but not as accurate as the Mantoux (intracutaneous) test.

Some experimental work now in progress promises a tuberculin-containing ointment which may be applied to the surface of the skin and which closely approaches in accuracy the Mantoux test. If this ointment proves satisfactory it will remove much of the previous objection to the tuberculin test and will permit tuberculosis workers to proceed with case-finding in much higher percentages of school-children and others than was previously possible. Another forward step is the provision being made by Health Departments to furnish free to physicians tuberculin properly diluted for immediate administration.

The second stumbling block has been the cost of X-ray films. If one wished to make a tuberculosis inventory of 25,000 school children or 10,000 university students, the cost of the X-ray films alone was stupendous. We are deeply indebted to Mr. Henry Wright, President, and Dr. Charles S. Prest, Secretary, of the Queensboro Tuberculosis and Health Association, for stimulating the interest of the Powers Brothers Company in the development of a paper film, which promises the possibility of making X-ray films in large numbers at a very low cost. These organizations, working in conjunction with the Bellevue-Yorkville Demonstration staff, have devised attachments and special X-ray equipment by which it is possible to make a thousand chest exposures in a single day with one machine.

In applying this case-finding method to university students, Diehl calls attention to examinations of 2,500 entering students in the fall of

1931. Among approximately 800 reacting positively to tuberculin and having X-ray-film examinations of the chest were found 15 cases of adult type of pulmonary tuberculosis in addition to many cases of pleurisy and childhood type of tuberculosis. One of the cases with adult type of pulmonary tuberculosis had advanced disease, five were moderately advanced, and nine were minimal. The control of these cases with reference to dissemination of tubercle bacilli on the campus, as well as individual treatment of the cases, is a service worth much more than it costs the institution and the student body. The fact that more than a half-dozen great American universities instituted similar tuberculosis-finding procedures in the fall of 1931 is of great significance.

So practical is this method of attack that sanatoria are beginning to employ full-time epidemiologists, whose duty it is to work with family physicians of patients admitted to their institutions in finding the source of their patient's disease. Moreover, they place under examination and observation those persons who have been in contact with their patient. This procedure at the Minnesota State Sanatorium is proving very effective.

Recent advances in collapse therapy are doing great good for individual patients, but a greater good by closing off lesions which otherwise would be sources of exposure to vast numbers of people. The discovery of the fact that many patients may remain ambulatory while artificial pneumothorax is being induced, or soon afterward, promises to do much to relieve congestion in rooms, wards, and hospitals for tuberculosis patients, to relieve the patient of economic strain, to relieve the taxpayer of a considerable burden, and to prevent the spread of tuberculosis. The chief problem is one of finding cases suitable for such treatment, that is, before the disease has become extensive and there is much breaking down of tissues. Past experience has taught us that unless such case-finding methods are used in order to detect the disease in the earliest possible stage, many are too advanced to respond well to any form of treatment. Therefore, we must not wait for patients to come to us with complaints, but must go out and find them months and even years before they would develop symptoms.

A summation of the facts of tuberculosis now at hand points to prevention of the initial and all subsequent infections as the goal for which we must strive. This means that pressure must be brought to bear on all the modes of attack on tuberculosis now in existence, so that each will function at the highest possible efficiency. The principal methods are all based on case-finding, so that the source of exposure may be stopped.

PULMONARY ROENTGENOGRAPHY OF SMALL EXPERIMENTAL ANIMALS

SIDNEY GREENBERG[1]

The roentgenological interpretation of pulmonary lesions in small laboratory animals, such as the rabbit, guinea pig and rat, is usually unsatisfactory. This is due to the relatively broad mediastinal shadow and the high position of the diaphragm which encroach on the pulmonary fields to such an extent that only a very small part of the lung is represented. The shadows of the scapulae are also within the lung field and the rapid respirations of these animals make it impracticable to attempt to take the picture at the most favorable point, the height of inspiration.

These obstacles have been overcome by the technique here described, which permits the interpretation of chest roentgenograms in these animals with the same degree of accuracy that obtains for human beings.

TECHNIQUE

The animal is held in the upright position, a procedure which lowers the plane of the diaphragm and narrows the mediastinum, thereby materially increasing the size of the lung fields visualized. The scapulae are drawn laterally, so that their shadows do not appear in the lung fields, by crossing the fore-legs of the animal at the level of the neck. The alignment of the sternum with the vertebral column in the postero-anterior position is made by locating the exact position of the bodies of the vertebrae by means of deep palpation over the upper abdomen just below the xiphisternum. The rapid respirations of the animal are controlled by gradually obstructing the nares, which deepens and retards the respirations. At the height of a deep inspiration the exposure is made.

Figure 1 shows the table with a casette-holder in position. The casette-holder is made of two broad flat pieces of wood (*A* & *B*) joined to form an *L*. The back of the vertical arm is covered by a lead plate (not visible in the cut) to protect the operator from excessive radiation.

[1] New York State Hospital for Incipient Pulmonary Tuberculosis, Ray Brook, New York.

The upper and lower edges are lipped to carry the casette (*C*) and a lead plate (*D*), which are held in position by a clamp (*E*) above. The lead plate (*D*) covers three-quarters of the casette (*C*), allowing for four separate exposures on each film. The upper corners of the film serve best for the laboratory number of the animal and the date the roentgenogram is taken.

Figure 2 illustrates the rabbit in position for a posteroanterior roentgenogram. The assistant on the left grasps the animal by the ears in his left hand and by the hind legs in his right hand, and places the animal in the upright position with its back against the casette. He should avoid grasping the animal about the abdomen which elevates the position of the diaphragm by increasing the intraäbdominal pressure. The assistant in the centre crosses the rabbit's fore-legs at the level of the neck. The assistant on the right determines the position of the scapulae and sees that the sternum and vertebral column are in alignment. He then controls the animal's respirations by slowly obstructing the nares, and makes the exposure at the height of inspiration.

Figure 3 illustrates the guinea pig in position for a posteroanterior roentgenogram. The fore-legs are drawn laterally and upward without being crossed; otherwise all procedures are the same as for the rabbit.

For lateral roentgenograms the rabbit is held by the ears and hind-legs upright, with its left chest to the casette. The fore-legs are held firmly above the elbow joint and pushed backward and upward, a procedure which raises the shoulders and draws the scapulae backward so that their shadows come to lie outside the lung field.

The roentgen tube is 30 inches from the casette for the rabbits and 25 inches for the guinea pigs. The amperage for both animals is 30 milliamperes; the voltage varies from 95 to 115 for the rabbits and from 90 to 100 for the guinea pigs, depending on the size of the animals. One-twentieth of a second exposure is used for both animals.

Chest roentgenograms are presented of a healthy rabbit in the posteroanterior exposure, as well as roentgenograms of rabbits presenting pulmonary lesions both in posteroanterior and lateral views. From a technical standpoint the serial roentgenograms of the rabbits are comparable with the usual serial roentgenograms of the human being and changes in the appearance and distribution of the shadows may be followed as readily in one as in the other. It should be possible with the present technique to follow very accurately the development of various pathological processes in the lung of the experimental animal and the

corresponding shadows in the roentgenogram. The technique might likewise be profitably employed in the study of experimental cardiac disease.

This work was undertaken at the suggestion of Dr. Harry A. Bray whose continued interest I wish to gratefully acknowledge. I am indebted to Miss Anna Sanlow for the preparation of the figures.

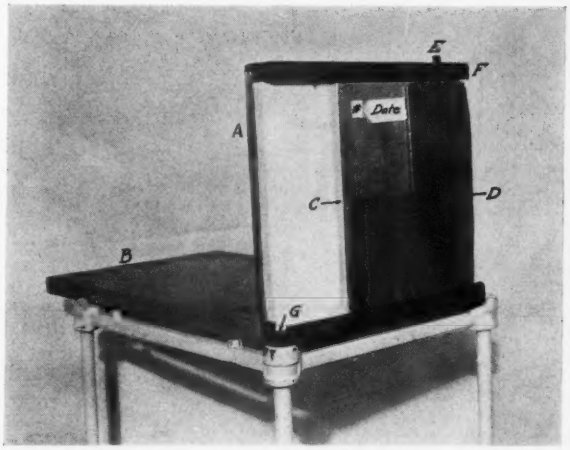


FIG. 1. Casette holder loaded with casette and lead plate in position for taking roentgenogram.

A: Vertical arm (14–13–1″), with one-inch overhanging upper edge (*F*) and one-inch groove (*G*) at base with one-half-inch lip.

B: Horizontal arm (25–14–1″).

C: Casette (8–10″ film) with three-quarters covered by lead plate (*D*). Exposed quarter has number and date in upper corners.

FIG. 2

FIG. 3

FIG. 2. Rabbit in position for taking posteroanterior roentgenogram

FIG. 3. Guinea pig in position for taking posteroanterior roentgenogram

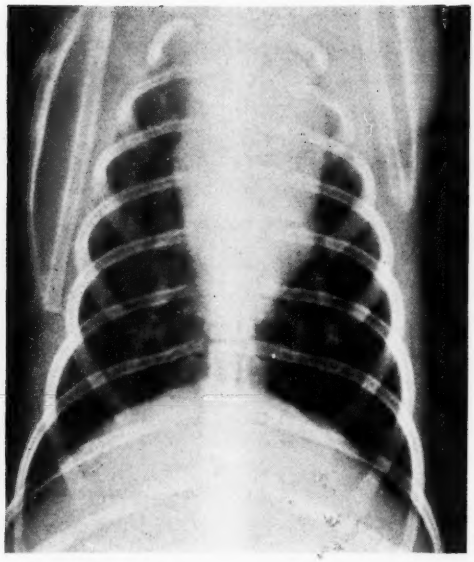


FIG. 4. Roentgenogram of normal rabbit

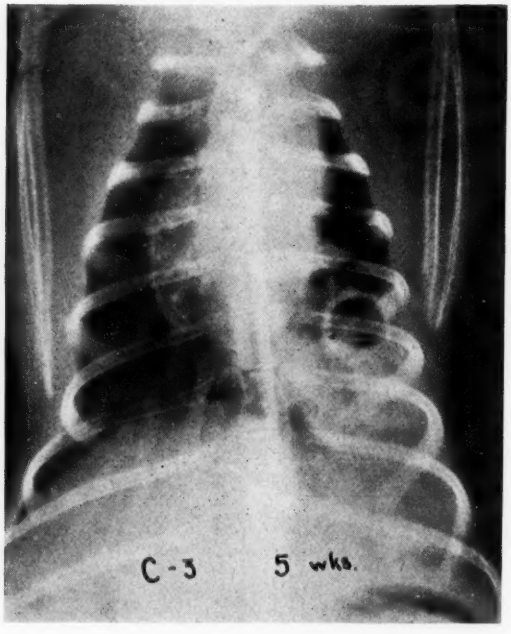


FIG. 5. Extensive disease at left base with cavity-formation (rabbit)

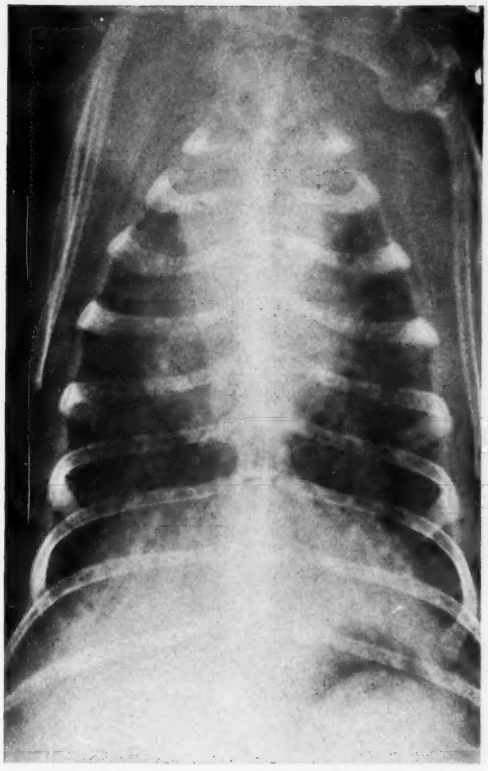


FIG. 6. Extensive bilateral mottling (rabbit)

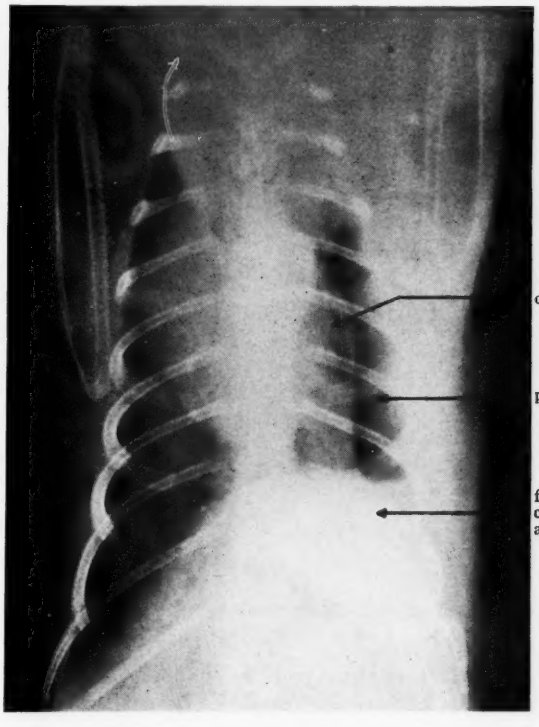


FIG. 7. Hydropneumothorax (rabbit)

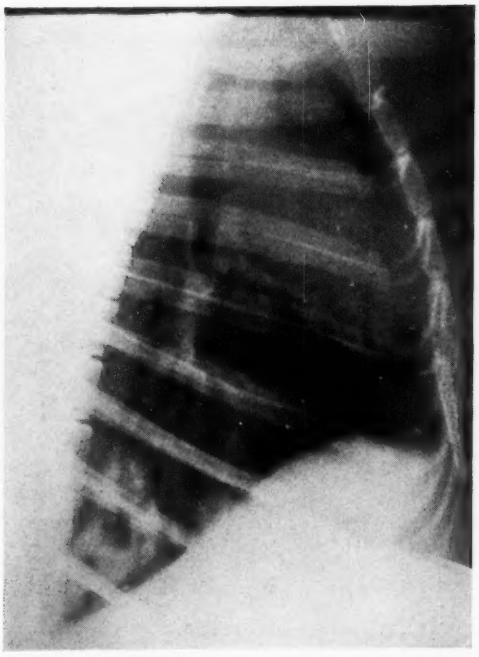


FIG. 8. Lateral roentgenogram of a rabbit in which the costophrenic sinus shows disease which was obscured by the diaphragm in the posteroanterior roentgenogram.

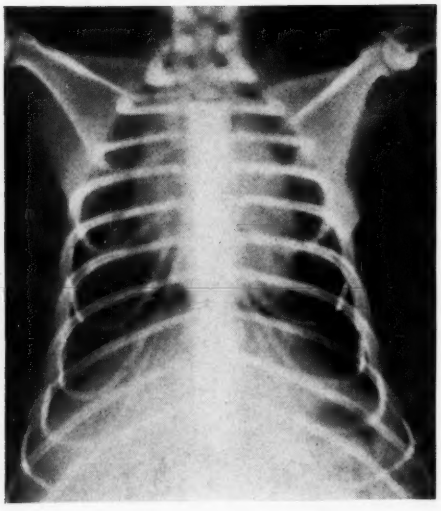


FIG. 9. Roentgenogram of normal guinea pig

LOCALIZED EXPERIMENTAL TUBERCULOSIS OF THE LUNGS[1,2]

ROBERT G. BLOCH

The possibilities of animal experimentation with pulmonary tuberculosis are limited by the lack of control over the localization and development of lung lesions by the investigator. Pulmonary inoculation with virulent tubercle bacilli commonly results in widely scattered lesions throughout the animal's lungs. This is equally true of secondary infections spreading from extrapulmonary inoculation and of intratracheal infection by the inhalation method. With adequate technique a fairly well-localized tuberculosis may sometimes be obtained by the intratracheal injection of a saline suspension of organisms. However, all these methods produce, even when small numbers of bacilli are introduced, progressive lesions with early (or preceding) involvement of other organs, and may result in death before the object of the experiment is attained. Only an attenuated strain like the R1 will produce well-confined single lesions, for instance, a macroscopic isolated primary complex, but without adequate control of localization and with a good chance that the lesions may either develop too little or heal too quickly to attain the purpose of the experiment. For example, lung-collapse experiments on tuberculous animals cannot be carried through a sufficient length of time, on account of the progressiveness of the lesion, and certainly not on tuberculosis of a particular nature and in a definite location. Similarly, it is hardly possible to produce isolated cavitation of an appreciable size remaining isolated for a considerable time by the usual methods of infection.

A method which facilitates experimentation of the aforementioned nature is herewith presented. It originated from other experiments, in the course of which attempts were made to localize very small amounts of lipiodol (40 per cent iodized poppyseed oil) in roentgenograms of animal lungs. The results are pictured in plate 1, which shows

[1] From the Department of Medicine, University of Chicago, Chicago, Illinois.

[2] Read at a meeting of the American Society for Experimental Pathology, Montreal, Canada, April, 1931.

roentgenograms of the lungs of four guinea pigs injected with different amounts of lipiodol; namely, G.P. A, with 1/10 cc.; G.P. B, 1/15 cc.; G.P. C, 1/20 cc.; G.P. D, 1/40 cc. The procedure of injection was to tie the animal firmly on a board, lift the trachea through an incision in the neck, and inject the oil through a short needle from a tuberculin

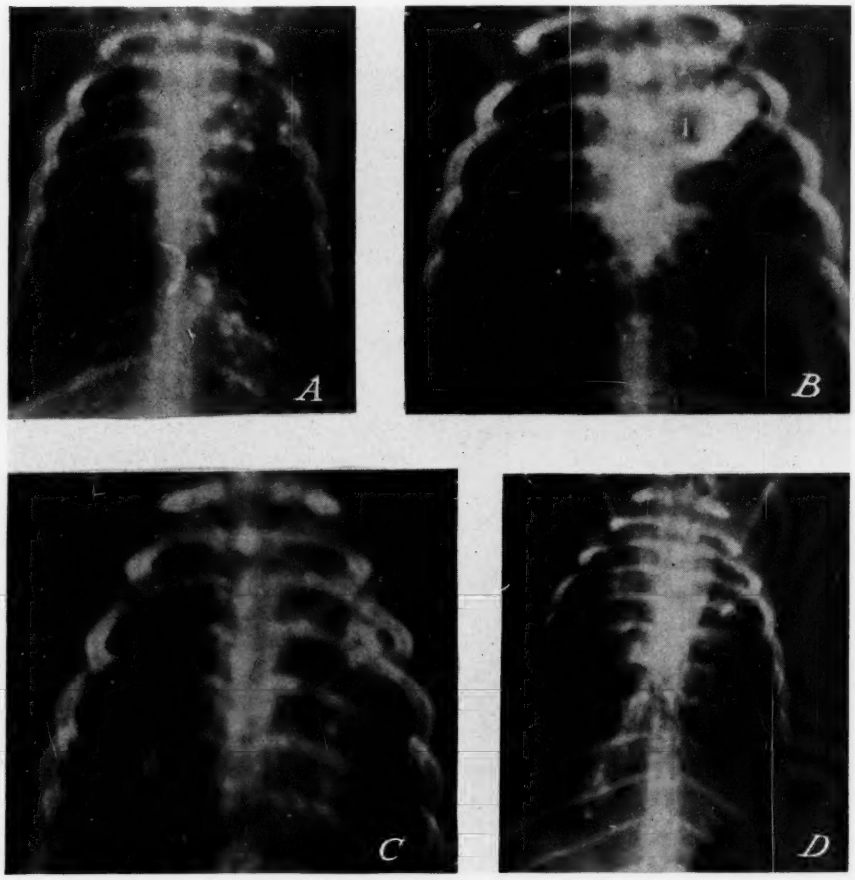


PLATE 1. For description see text

syringe. The oil was heated to 40°C. to lower its viscosity and make it proceed to the alveolar spaces quickly (2). During the injection the animal board was held in an upright position at an angle of 45 degrees toward the right side and was left in that position for ten minutes following the injection. (Horizontal position with the animal lying on the side results in gulping and ingestion of the oil.)

It will be noted that in all four animals the greater part of the oil is located in the subapical area of the lung field. In G.P. A (1/10 cc.) an overflow of oil settled in the right lower lung field. In G.P. B (1/15 cc.) there was a massive accumulation of oil in the upper lung field. G.P. C (1/20 cc.) shows a peripheral oil collection, with a slight overflow into the basal lung field, while in G.P. D there is a well-isolated small accumulation of oil in the same area.[3]

The idea occurred that a very small drop of lipiodol, like that in G.P. D, could be loaded with tubercle bacilli, and that the oil would probably confine the organisms well within the injected area and at the same time by its roentgenographic effect reveal the site of the future tuberculous involvement immediately after injection, if a lesion were to develop at all. A suspension of 10 mgm. of moist tubercle bacilli of the virulent human strain H119 in 5 cc. of lipiodol was prepared and a very even distribution of the organisms in the oil obtained by the addition of a drop of sodium phosphate (3). Of the suspension containing 1/20 mgm. of the bacilli, 1/40 cc. was injected into the right lung of 6 guinea pigs by the described method. Four control guinea pigs were injected by the same method and with the same amount of organisms suspended in 1/40 cc. of saline solution. Roentgenograms of the chest of the oil-infected animals were made immediately after inoculation. In four of these a well-localized oil accumulation near the periphery of the right subapical region, as shown in figure A of plate 2 was found, while in two animals the oil was scattered in a few very small droplets through the same area. The 6 oil-infected animals showed no sign of disease during four weeks following infection, while the control animals began to lose weight after three weeks.

All guinea pigs were killed after four weeks. In all of the oil-infected animals tubercles were found in the right upper lobe. In 4 animals there was only one tubercle. In one, a large tubercle and two additional small ones were found, while five small tubercles were found in another guinea pig. All lesions were localized in the right upper lobe. In three of the

[3] Nearly 100 animals, mostly rabbits and guinea pigs, received intratracheal injections in this and other experiments. It is noteworthy that in the small animals placed in a right-angle position the bulk of the oil invariably settled in the right subapical lung region, which on postmortem examination was identified as belonging to the right upper lobe. In the left-angle position the bulk of the oil always settled in the upper part (apex) of the left lower lobe which on the roentgenogram presents itself as the perihilar area. The great consistency of these findings throws an interesting light on the localization of bronchogenic tuberculous lesions. This question will be discussed elsewhere.

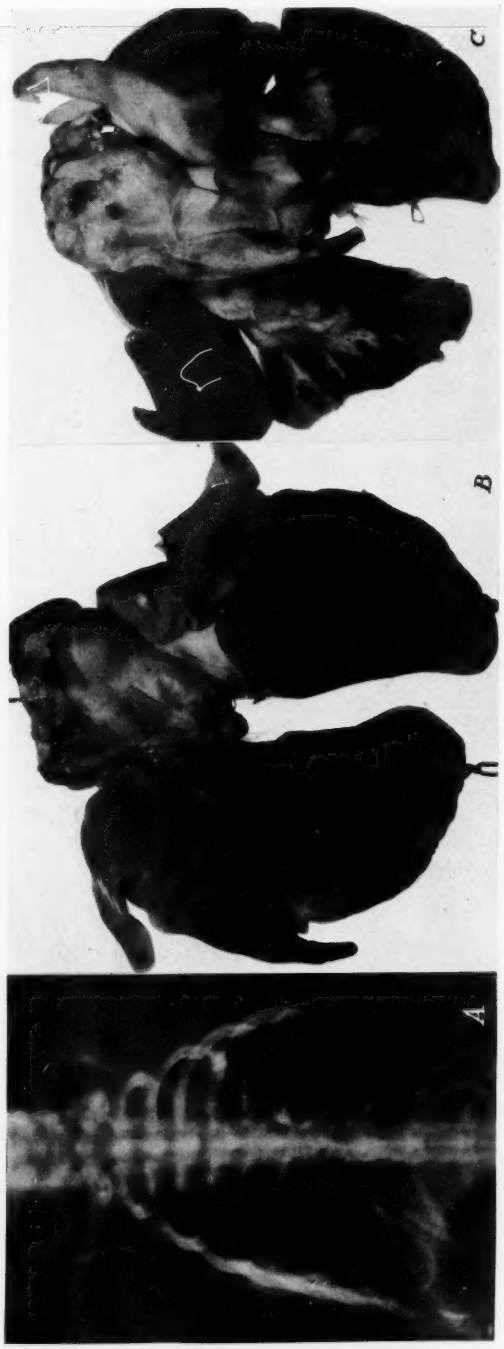


PLATE 2. For description see text

lungs an isolated large tubercle was found on the surface similar to the one in figure B of plate 2, showing the lesion which developed from the oil drop in roentgenogram A. All animals had extensive enlargement of the tracheobronchial lymph nodes on the right side. The spleen and liver were not involved. Figure C of plate 2 shows the lung of one of the guinea pigs infected with the saline suspension. There was a widespread massive tuberculosis of both lungs, with bilateral involvement of the tracheobronchial lymph nodes in all 4 animals. The right upper lobe was the most involved part in these guinea pigs also. In the guinea pig shown in figure C, this lobe was taken up completely by a tuberculous lesion with beginning caseation. In all of the four control guinea pigs numerous tubercles were found in the spleen, and in two of them in the liver as well.

A method of experimental infection, in which the carrier of virus is apt to produce tissue changes, can by itself be of only limited value for histological studies of the produced infection. Corper (5) has pointed out that oils produce bronchopneumonic processes in the lung parenchyma, and Brown (4) found a monocytic reaction in the tissues, the monocytic cells ingesting and carrying away the oil droplets from the invaded areas. The writer can corroborate his findings on the basis of his own experiments, and widen them to the extent that a monocytic reaction becomes noticeable in the blood of most patients after endobronchial lipiodol injection. This observation deserves particular attention in view of the importance which has been attached to the monocyte in the study of tuberculosis during recent years. The formation of fibrosis has also been reported as a later result of oil in the lung tissue (5); therefore, experimental tuberculous infection with lipiodol as a carrier of the bacilli cannot be recommended for histological investigations.

The oil changes the macroscopic and clinical aspects of tuberculosis in so far as it confines the bacilli to a limited area, thereby localizing the process and at the same time intensifying it by the comparatively large number of bacilli in one place (cavity-formation). However, this effect of oil confinement is undoubtedly reduced by the definite destructive influence which the oil has on the bacilli. The causes of this damage do not seem to be clear. The lack of oxygen may be partly responsible for a reduced multiplication of the organisms within the lung tissue. Archibald and Brown (1) have pointed out that, with the alveolus only partially filled with oil, the supply of oxygen must be diminished. Involve-

ment of other organs and secondary dissemination in the lungs occur very late, and not at all if small numbers of bacilli are introduced. An added stimulation of fibrosis by the oil may help to prolong the localization and be particularly responsible for the slow spread of the lesions. For prolonged experimentation with pulmonary tuberculosis the oil-carried infection furnishes very good possibilities, and offers the additional advantage of exact localization as well as of verifying the localization of the infection immediately following the introduction of the bacilli.

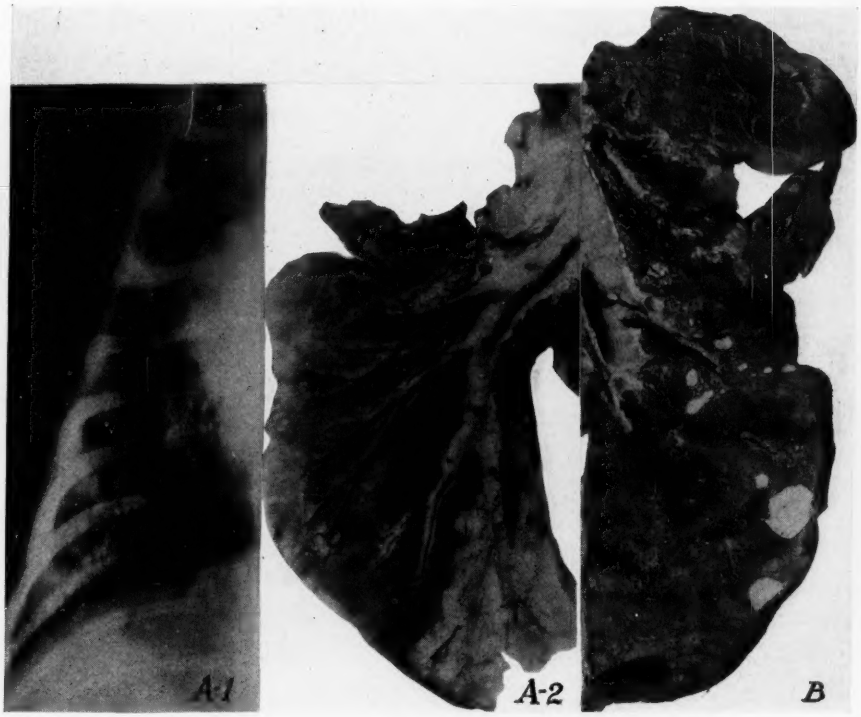


PLATE 3. For description see text

The conclusion may well be made that the method could be employed for the experimental production of localized tuberculosis in other organs and should also be tried with other pathogenic organisms.

In plate 3, the results of a lipiodol-carried infection in goat's lungs is shown. The inoculations were made for the purpose of a local mechanical experiment on basal tuberculosis. One milligram of a virulent bovine strain was injected in 2 cc. of lipiodol. Figure A-1 shows the roentgeno-

gram of a goat's lung with the lipiodol in the right lower lobe. The animal was killed six weeks after injection and a well-localized tuberculosis was found in the injected area with involvement of the regional lymph nodes (figure A-2). Another goat's left lung is shown in figure B. The injection was again made into the lower lobe. The animal showed no signs of disease at any time after the infection and was killed after one year. There were two large isolated tuberculous lesions at the periphery of the injected area and a few smaller ones scattered through the upper part of the lower lobe. All of these foci were in a state of partial calcification. There was no secondary tuberculous involvement of other organs in either goat.

SUMMARY

A method for the experimental production of localized pulmonary tuberculosis is described. It consists of the introduction of the bacilli suspended in iodized oil which permits roentgenographic control of the localization of the infection. The method allows the production of localized primary tuberculous complexes with virulent bacilli. It can be used with advantage for experiments requiring slowly progressive lesions with late secondary involvement. Its value for histological studies is limited.

REFERENCES

(1) Archibald, E., and Brown, A. L.: Dangers of introducing iodized oil into the tracheobronchial system, Jour. Am. Med. Ass., 1927, lxxxviii, 1310.

(2) Bloch, R. G.: The viscosity of lipiodol in bronchography, Am. Jour. Roentgenol. & Rad. Ther., 1932, xxvii, 847.

(3) Blumenberg, W., and Wienig, H.: Betrachtungen und Versuch zur Bestimmung der Keimzahl in tuberkelbazillen Kulturen, Ztschr. f. Tuberk., 1928, li, 417.

(4) Brown, A. L.: The fate of iodized oil (lipiodol) in the lungs, Surg., Gyn. & Obst., 1928, xlvi, 597.

(5) Corper, H. J., and Freed, H.: The intratracheal injection of oils for diagnostic and therapeutic purposes, Jour. Am. Med. Ass., 1922, lxxix, 1739.

A COMPARISON OF THE PATHOLOGICAL CHANGES IN EMBOLIC TUBERCULOUS AND PYOGENIC PULMONARY ABSCESSES[1]

An Experimental Study

PHILIP H. PIERSON

The object of this paper is to present the pathological findings in two series of pulmonary abscesses produced in dogs by the introduction of infected emboli, the tuberculous series having been produced by infection with tubercle bacilli H37 and the pyogenic group having resulted from emboli containing varying combinations of nonhaemolytic streptococci, *Staphylococcus aureus* and *B. coli*. The production of these abscesses was planned and carried out by Drs. Holman, Chandler and Cooley and fully described in *Experimental Studies in Pulmonary Suppuration*, printed in *Surgery, Gynecology and Obstetrics*, March, 1927. Briefly, their technique was as follows:

With the dog under ether anaesthesia, his jugular vein was exposed and a small piece excised, one end of which was tied with silk and through the other end the desired culture of bacteria and a paraffine-coated shot were introduced and this end similarly tied. This embolus was introduced into the proximal end of the exposed vein and the wound closed. The presence of the lead shot enabled them to localize at once the position of the embolus in a roentgenogram and to follow its appearance in comparative pictures. It is unfortunate that vital staining was not incorporated in their work, for it would have helped materially in differentiating certain cells,—noticeably large mononuclear cells (wandering cells) and fibroblasts.

In this regard it is interesting to note, in a recent publication by Sabin (1) (2), quoting Lewis and Lewis, Carrel and Ebeling, and Parker, that there is apparently a similarity between the fibroblast, monocyte and macrophage (clasmatocyte) and epithelioid cell, representing different functions of the same cell. Fried (3) feels that the large mononuclear cell originates from the alveolar epithelium and plays the rôle of defense

[1] From the Laboratory for Surgical Research, Stanford University Medical School, San Francisco, California.

and metabolism. In the following descriptions this cell will be especially noted and the rôle it plays at that particular time.

CHRONOLOGICAL STUDY OF TUBERCULOUS AND PYOGENIC EMBOLIC ABSCESSES

Tuberculous

Six hours: The first tuberculous embolic abscess was studied at six hours and there was found a moderate engorgement of all the blood-vessels, with a slight polymorphonuclear infiltration. If the sections had been stained for tubercle bacilli, we might have expected the leucocytes to have shown evidence of phagocytosis of the bacilli, according to the recent work of Vorwald (4). The interstitial tissue was thickened and many large mononuclear cells were evident in this tissue. Many had protoplasm evident about their nuclei but there were also nuclei with no evidence of a surrounding membrane. (Plate 1.)

Twenty-four hours: At twenty-four hours there were a few small areas of pneumonitis surrounding the embolus. The blood-vessels were engorged and contained many polymorphonuclear leucocytes. The interstitial tissue and, to a less degree, the alveoli contained many large mononuclear cells. (Plate 1.)

Pyogenic

Twenty-four hours: The dog that received this embolus died twenty-four hours after its introduction and the lung showed a marked haemorrhagic infarction. About this was an extensive area of bronchopneumonia. Blood-vessels were greatly engorged and the walls of alveoli destroyed and the spaces filled with red blood cells and a relatively small number of polymorphonuclears. Scattered throughout this area and particularly at its periphery were many large mononuclear cells, most of them showing no protoplasm. There were numerous small round cells, and nuclei of all sizes between these and the size of the typical large mononuclear nuclei. It is interesting to note the appearance of the same cells as a response to the pyogenic and the tuberculous infection, but the reaction in the tissue was much more severe and haemorrhagic in the pyogenic than in the tuberculous infection. (Plate 1.)

Tuberculous

Five days: Two sections were studied at this interval. In one the lobe which was infected was excised at this time. There were scattered

areas of increased vascularity and extravasation of blood into the interstitial tissue. Here also were seen small lymphocytes and many large mononuclear cells. No necrosis or localization of the infection was seen in this specimen but another of the same duration showed rather marked necrosis. This difference may be due to the fact that the first animal had previously received a tuberculous embolus and the lobe in which it lodged had been excised. In the specimen with the more extensive lesion there was also present a marked infiltration with large mononuclear cells, those at the periphery of the infection rarely possessing protoplasm, while those closer to the centre showed a definite cell membrane in many instances. In one area there was a definite tubercle formed by these large nuclei. The cellular reaction, where there was necrosis, was composed of polymorphonuclear leucocytes, small round cells and wandering cells, more often possessing protoplasm than those in the surrounding tissue, suggesting that they developed protoplasm as the need for phagocytosis increased. (Plate 2.)

Seven days: A large infarct was present with a fairly sharp line of demarcation. Along the border of this the interstitial tissue was infiltrated with small and large mononuclear cells, and here again very little protoplasm was seen. Toward the centre of the infarct these large mononuclear cells at times had protoplasm. There were also small round cells, polymorphonuclear leucocytes and many new blood-vessels. (Plate 2.)

Pyogenic

Four days: Two dogs died four days after the introduction of pyogenic emboli. There were present bronchopneumonic areas containing a similar cellular reaction: the interstitial tissue was infiltrated with the same granular nuclei, varying in size, surrounded by very little protoplasm. There were only a few polymorphonuclears, and no cavity was seen. The pleural thickening over the area was twenty to twenty-five times the normal thickness, and here the nuclei, having the same appearance as the large mononuclears, were associated with fibrils. The similarity of the nuclei raises the question as to whether they were of the same origin as the large mononuclear cells. (Plate 2.)

Six days: Here a large cavity was present, with a haemorrhagic infarct distal to it. In this necrotic area there were engorged blood-vessels, small round cells, polymorphonuclears and a moderate number of large mononuclear cells. The nuclei were rarely surrounded by oval protoplasm, but there were fibrils so often associated with these nuclei that

evidence of repair was marked both microscopically and macroscopically. (Plate 2.)

Summary of the First Week

To summarize the progress of these two types of infection at the end of the first week: It was evident that in the tuberculous series the infection began as an interstitial infiltration of leucocytes and large mononuclear cells, and progressed to haemorrhagic infarction without marked cavity-formation. In the pyogenic series three out of four of the dogs died from their infection. There was a marked haemorrhagic infarction within twenty-four hours, which progressed to a large cavity showing evidences of considerable walling-off by fibrous tissue and pleural thickening overlying the cavity. The same cellular reaction was present as in the tuberculous series, the polymorphonuclears being present in the necrotic areas and the large mononuclears infiltrating the tissue as phagocytes and possibly later as fibroblasts.

Tuberculous

Ten days: The density of the infarct seen three days previously had disappeared, with the development of a cavity and clearing of much of the central debris. Some polymorphonuclear leucocytes were seen near the centre of the cavity, while through all the infiltrated tissue there were a great many of the wandering cells, possessing protoplasm which contained vacuoles and bits of foreign material. They were apparently phagocytic to a marked degree, as they had replaced the previous haemorrhagic area, and their intact protoplasm during this function was in contrast to the lack of protoplasm about the nuclei in the interstitial tissue surrounding the cavity. Between the centre and periphery of the cavity there were fibroblasts whose nuclei resembled very closely those of the wandering cells. (Plate 3.)

Thirteen days: The lobe containing this embolus and its resultant infection was resected at this time. There was a small area of necrosis, and the interstitial tissue everywhere contained a moderate number of small round cells and many large mononuclear cells, whose protoplasm in most instances was intact. It was also interesting to note that nuclei were seen whose general appearance was that of large mononuclears but in an elongated and bent form, suggesting a transition stage toward that of fibroblasts. (Plate 3.)

Pyogenic

Eight days: A haemorrhagic infarct was present with an area of central necrosis. In the necrotic area pus cells were numerous, while in the zone surrounding this there was an infiltration of small round cells and nuclei of the large mononuclear type. (Plate 3.)

Nine days: The lobe containing this embolus and infection was removed at operation and showed a well-walled-off cavity. The apparently normal tissue surrounding this area was infiltrated for some distance with small round cells. In the tissue of the cavity-wall there was an infiltration of small round cells, large mononuclear nuclei and an occasional pus cell. The blood-vessels were dilated and new vessels were being formed. A definite infiltration of fibroblasts was evident, and in places their nuclei were markedly flattened and dense, and the appearance of a fibrous wall was quite marked. At one place the cavity was seen rupturing into a bronchus and columnar epithelium seemed to be growing in and partly lining this communication. (Plate 3.)

Thirteen days: The dog possessing this pulmonary abscess died on the thirteenth day following the introduction of the embolus. A moderate-sized abscess was present, surrounded by a dense wall of fibrous tissue. In the inner part of this wall there were many well-preserved wandering cells, whose protoplasm was intact. Their nuclei on the whole were smaller than those of the same type of cells previously described. Small round cells were also present in large numbers. In this specimen there were portions of the cavity surface lined with cuboidal epithelium. From the findings in the previous section, it was evident that this had grown in from the lining of the bronchus. (Plate 4.)

Summary of the Second Week

Cavity-formation was evident in both the tuberculous and pyogenic groups and the infection was the cause of death in one of the three dogs in the pyogenic series. The large mononuclear wandering cells had been present in considerable numbers in both infections and their function had been largely phagocytic. It was also a possibility that the fibroblastic proliferation had also arisen from this source. The small round-cell infiltration was quite marked in each series. They, too, probably exerted an influence on the infection, perhaps not phagocytic but possibly chemical. The process of repair had progressed further in the pyogenic infections, and on the thirteenth day epithelium was lining several portions

of the cavity-wall. Pus cells were present toward the inner wall of the cavity. Nothing was characteristic of a tuberculous infection during this, the second week of the disease.

Tuberculous

Sixteen days: The process was not as advanced in this specimen as in the previous one. At least, there was some necrosis but not a true cavity. This may have been due to the fact that the animal had had a previous tuberculous embolus seventy-nine days before and the lobe had been excised on the thirty-fifth day. The areas of necrosis were infiltrated with small round cells which seemed to form zones about the areas of debris. Large mononuclear cells with and without protoplasm were also present. Many without protoplasm were seen in the debris, while those with protoplasm were evident in the thickened interstitial tissue. This apparent reversal of type may have been one explanation for the sluggishness of the reaction. Almost no pus was seen. Fibroblasts were present but in no definite walling-off arrangement. (Plate 4.)

Seventeen days: There was an extensive area of true tuberculous tissue in this specimen. Single and conglomerate tubercles were evident for the first time. These tubercles were composed of concentrically arranged, large mononuclear or epithelioid cells about a clear centre, while about their periphery there were many small round cells. Fibroblasts were evident surrounding these tubercles in an effort at repair, although there was but little caseation present. (Plate 4.)

Twenty-three days: The lobe containing this tuberculous abscess was removed twenty-three days after the introduction of the embolus. There was a large area of diffuse necrosis and caseation, within which were many small tubercles and some scattered areas of fibrosis. The inner wall of the abscess was composed of caseous material and pus cells, while a little deeper in there were many large mononuclear cells, most of them possessing protoplasm. The interstitial tissue for some distance from the cavity was infiltrated with pus cells and large mononuclears. (Plate 5.)

Twenty-five days: The animal was killed twenty-five days following the introduction of this tuberculous embolus. There was present a large multilocular cavity, surrounded by a wall of conglomerate tubercles and caseous material. In this caseous material, which was not extensive, there were many pus cells and small round cells and a moderate number of large mononuclear cells. Fibrosis had definitely set in and in the

surrounding zone there were still many wandering cells without protoplasm. It now appeared that the active stage of destruction had ceased and hence there was less need for phagocytic cells, the walling-off process being accomplished by small round cells and fibroblasts. (Plate 5.)

Pyogenic

Sixteen days: The lobe containing this infection was excised sixteen days after the introduction of the embolus, the animal having made a clinical recovery before lobectomy was performed. There was no cavity present but the general appearance was that of an interstitial pneumonia. This infiltration consisted of fibroblasts with oval nuclei and in places more flattened nuclei and small round cells. In some instances these cells were present in the walls of the alveoli. The pleura overlying the infected area was markedly thickened by fibrin and immature fibroblasts. Very few leucocytes or wandering cells were seen. (Plate 4.)

Twenty-one days: Clinical recovery had taken place from the infection caused by this embolus before the lobe in which it lodged was removed on the twenty-first day. There was a small abscess-cavity entirely surrounded by a wall of fibrous tissue and very little reaction in the tissue. In places the interstitial tissue contained small round cells and a number of large mononuclear-cell nuclei without protoplasm, their shape suggesting young fibroblasts. (Plate 4.)

Summary at the End of the Twenty-Fifth Day

Definite tubercles were first seen on the seventeenth day and they were composed of epithelioid or wandering cells with a surrounding zone of small round cells. Large mononuclear cells with vacuoles were evident, beginning on the tenth day but particularly noticeable in the sixteen- and twenty-five-day-old specimens, and by the twenty-fifth day the virulence of the infection was subsiding and repair was well on its way. In the pyogenic group, too, the virulence of the infection was less severe, the animals clinically recovering. By the twenty-fifth day the cavity was surrounded by a more definite fibrous wall than was present in the tuberculous series. Small round cells and large mononuclear cells predominated. There was a similarity in appearance between the wandering cell nucleus and that of the fibroblasts in its different stages of maturation.

Tuberculous

Thirty-five days: The left lower lobe containing this infection was excised on the thirty-fifth day following the introduction of the tuberculous embolus. There was present a fairly extensive area of caseous pneumonia with central abscess-formation. There was also a bronchitis and peribronchitis and considerable infiltration of the surrounding interstitial tissue. In a number of places whorls of fibrous tissue were seen surrounding small central zones of caseation,—the remnants of previously more active tubercles. There were still some earlier tubercles composed of epithelioid cells with a surrounding zone of small round cells and fibroblasts. Vacuolated wandering cells were still present, but small round cells seemed to dominate both in the caseating area and in the surrounding tissue. (Plate 5.)

Forty-one days: This lobe was resected forty-one days following the introduction of the tuberculous embolus, and a fairly well-walled-off, caseating cavity was seen. In the centre of the cavity some polymorphonuclears were seen, while a little deeper in the tissue an area of tubercles with concentrically arranged epithelioid cells was found. These tubercles were surrounded by fibrous tissue in varying stages of development. The wandering-cell protoplasm was not as well demarcated as in the previous sections. Considerable small round-cell infiltration was evident both centrally and in the surrounding tissue, and many new blood-vessels had made their way into all the tissue. Again it was interesting to note the similarity of the nuclei of the wandering cells and the fibroblasts. (Plate 6.)

Fifty-one days: The lobe containing this embolus and its resulting infection was excised on the fifty-first day and an abscess-cavity was seen surrounded by a denser wall of fibrosis and many new blood-vessels. In the caseated area the polymorphonuclears were seen associated with many small round cells and a number of wandering cells. There was present a type of nucleus in these cells not so evident previously, that is, the nucleus possessed a concentration of the chromatin into a definite nucleolus. This transition was probably associated with the function to be performed at this stage,—diminishing phagocytic work and increasing repair, for the fibroblastic function had progressed to a considerable degree. (Plate 6.)

Ninety days: It is interesting to note that this dog had previously received two tuberculous emboli, the infected lobes removed at thirty-

five- and sixteen-day intervals respectively, and that following the removal of the lobes carrying this infection the dog lived eighty-three days.

The cavity at this stage contained but very little caseous material and was fairly well walled off by a noncompact band of fibrous tissue. The cellular infiltration was of two types,—small round cells and large mononuclear cells. The small round cells were dispersed throughout the tissue rather uniformly with no localized arrangement. The large mononuclear cells were evident at the centre, both with and without protoplasm, the latter performing whatever phagocytosis remained to be done. A little deeper into the wall the same-appearing nuclei with small strands of protoplasm suggesting fibroblasts were seen. In areas these fibroblasts were so dense that they represented real fibrous tissue. In the interstitial tissue there was still a moderate infiltration with small round cells and large mononuclear cells. (Plate 7.)

Ninety-two days: The lobe bearing this infection was resected ninety-two days after the tuberculous embolus was introduced. There was present a thin-walled, moderate-sized cavity, this wall containing closely packed, darkly staining fibroblastic nuclei with heavy fibrous protoplasm. Some small round cells were scattered in this wall and in the immediately surrounding tissue, suggesting possibly a little focus not quite extinct. The surrounding alveolar walls seemed slightly thinned and distorted by the contraction of the fibrous tissue. This emphysema, seen clinically at postmortem and during life, represents a real problem that is outside the scope of this paper. (Plate 7.)

Pyogenic

Thirty-three days: Lobectomy was performed thirty-three days after the introduction of the pyogenic embolus. The animal had made a clinical recovery before operation. Here the process was somewhat more active than in the twenty-one-day specimen. The cavity was surrounded by a wall of less-developed fibrous tissue, the central part showing polymorphonuclears, small round cells and large mononuclear nuclei. Then were noted zones of early fibroblasts, small round cells, polymorphonuclears and large mononuclears, some more-developed fibroblasts and, finally, in the interstitial tissue, there was a moderate infiltration with large mononuclear nuclei. (Plate 5.)

Forty days: This dog was killed forty days after the introduction of the pyogenic embolus. He had made a complete clinical recovery. There was a cavity surrounded by a thin wall of fibrous tissue. In general,

the nuclei were flattened and darkly staining as were the fibrils, but occasionally oval, lighter-staining nuclei, resembling those of the wandering cells, were evident. (Plate 6.)

Sixty-two days: Lobectomy was performed sixty-two days following the introduction of the pyogenic embolus and the dog had clinically made a good recovery from the infection. Here again the reaction to the infection was very poor. At this interval after infection there was a large haemorrhagic infarct with central cavity-formation and a surrounding zone of bronchopneumonia. In the centre of this there were many pus and blood cells, small round cells and débris, while a little further away from the centre there were many large mononuclear nuclei,—often with two nuclei and possessing a spindle-shaped protoplasm. Where the débris was not too thick there was a moderate number of wandering cells and in the interstitial tissue were the large nuclei without protoplasm. Lining one portion of the cavity near its exit into a bronchus, there was some columnar epithelium, evidencing the manner in which cavities become covered with epithelium. (Plate 6.)

Sixty-three days: The animal was not ill at any time during the course of his infection and was killed on the sixty-third day of the disease. There was present a small cavity with a few faintly-staining, large nuclei in the centre, surrounded by a compact wall of fibrous tissue. The pleura over the abscess showed considerable thickening. The surrounding lung was normal. Here healing had progressed to the same degree as was present at the end of ninety-two days in the tuberculous series. (Plate 7.)

Summary of the Progress from the Twenty-Fifth Day to the End of Each Series

In the tuberculous series there was a fairly steady progress in the development of diffuse fibrosis beginning as whorls of fibrous tissue about the tubercles and finally blending into a compact fibrous wall. The cells taking part in this were the small round cells and the large mononuclear cells. The former seemed to have a part in the attack on the infection, while the latter were phagocytic and possibly the same cell from which developed the fibroblasts.

In the pyogenic series the same general plan was carried out except for the fact that it was more irregular in its progress. At forty days the fibrous wall was almost as compact as at sixty-three days, while at sixty-two days the progress resembled that present thirty-three days after

infection. Pus cells were present in both series where there was necrosis and in the pyogenic series they permeated the tissue to a greater distance, but the most active phagocytic work was carried on by the large mononuclear cells. The possible transition of these cells into fibroblasts is worthy of consideration.

DISCUSSION OF THE TUBERCULOUS SERIES AS A WHOLE

1. Pathological changes were noted as early as six hours following the infection of the embolus,—hyperaemia and interstitial thickening.

2. Marked changes were produced in all animals of the above protocols, the amount of the change varying, in the majority of cases, with the time-interval elapsing between the introduction of the embolus and the examination of the lung. These changes ranged all the way from a hyperaemia, bronchopneumonia, haemorrhagic infarct, tubercle-formation with caseation and cavity-formation, to an entirely healed process.

3. At six hours the interstitial infiltration consisted of polymorphonuclear and large mononuclear cells, while later the pus cells were more evident about the caseating area and the large mononuclears were scattered from the centre of the cavity to the interstitial tissue surrounding the inflammatory area. These cells were seen with and without protoplasm, the latter suggesting that in that stage they may be either in an early stage of formation or exerting a chemical action on the disease, while the presence of protoplasm classified them as highly phagocytic. Between the sixteenth and twenty-fifth days the protoplasm of these cells contained many vacuoles and at about fifty-one days there was a tendency for concentration of the chromatin in the nucleus to form a definite nucleolus. The similarity of the nucleus of this large mononuclear cell with that of the fibroblast at least raises a suspicion that they were of the same origin, and that the stage of the infection and the work to be done by that particular cell determined its appearance. I have no explanation for the above findings but present their occurrence. The rôle of the small round cell increased from about the seventh day through the periods of necrosis, excavation and fibrosis. They were present in small numbers even in the final stage of healing.

4. The first evidence of abscess-formation was noted at seven days while the first extensive tuberculous abscess was noted at twenty-three days.

5. The first typical tubercles were noted at seventeen days, although a tubercle composed entirely of large mononuclear cells was seen at five days.

6. Early in the series a tendency toward considerable interstitial thickening was noted and this tendency persisted throughout the series.

7. Pleural thickening occurred early and was a constant feature throughout the series, the amount of pleural involvement varying greatly, however.

8. Beginning with sixteen days, a bronchitis and peribronchitis were prominent features throughout the series.

9. No explanation is offered for the absence of giant cells.

10. Beginning with the first evidence of a tuberculous process on the seventeenth day and continuing through the series, there was a preponderance of granulation tissue over real caseation in most cases. Fibroblasts were evident as early as the tenth day.

11. At ninety-two days complete healing had taken place. A large cavity was present with a definite but thin wall of fibrous tissue and but very slight evidence of any inflammation.

DISCUSSION OF THE PYOGENIC SERIES AS A WHOLE

1. The introduction of pyogenic emboli into the venous circulation of the dog produced widely varying results, both as to the extent of the resulting process and the time necessary for its development. Extensive haemorrhagic infarction occurred as early as twenty-four hours with the death of the animal, while in other instances only a mild bronchopneumonia was found at much later dates; also abscess-formation occurred as early as six days in some specimens, while in others there was only an engorgement of blood-vessels and slight pleural thickening at sixteen days.

2. Polymorphonuclear leucocytes were more evident in this than in the tuberculous series.

3. The first abscess-formation was noted at six days.

4. Pleural involvement was prominent throughout the series.

5. The tendency to fibrous proliferation was also noted throughout the series, but was not as prominent a feature as in the tuberculous process.

6. There was a marked tendency for death to occur early in the process if at all. All deaths occurred during the first thirteen days; dogs passing this period recovered clinically even though extensive abscesses were found later upon examination.

7. In at least one case (dog H_2-13 days) there was epithelialization of the cavity-wall with low cuboidal epithelium.

SUMMARY

1. A more regular sequence in the state of infection was evident in the tuberculous infections, the lesions varying according to the time allowed for their development, while in the pyogenic infections an irregular course of events took place.

2. While there were more pus cells scattered through the tissue in the pyogenic infections, the same large mononuclear cells were evident as phagocytes in each series. Their nuclei were sometimes surrounded by no visible protoplasm, while in other areas the protoplasm contained many fragments of phagocytosed material—(see two cells in central upper portion of microphotograph "Ten days after tuberculous embolus," plate 3). The apparent similarity of the nuclei of wandering cells and later, as early and then more advanced fibroblasts, raises the question of their common source. Vital staining was not done in this work, so no definite conclusion can be drawn. Small round-cell activity as an adjunct to the large mononuclear cells was evident in both infections. It is quite possible that chemical, phagocytic and repair work was done by different stages of cells, all arising from one or two sources.

3. Abscess-formation occurred earlier as a rule in the pyogenic infection. However, it occurred with greater frequency in the tuberculous infection.

4. Pleural thickening was marked throughout both series.

5. Bronchitis and peribronchitis were prominent features throughout both series, occurring earlier in the pyogenic infection, but persisting longer in the tuberculous series.

6. The tendency for fibrous proliferation was noted in both series, but more marked in the tuberculous infections.

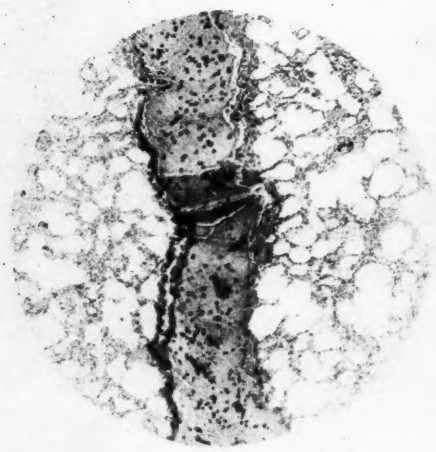
7. Epithelialization of the cavity was definitely noted in one instance, —thirteen days after the pyogenic infection. This may be one factor in the nonhealing often encountered clinically when pyogenic abscesses are treated by collapse therapy.

8. Complete healing took place in some instances following both pyogenic and tuberculous infections. The thin, firm wall present about the cavity in the ninety-two-day tuberculous infection may well represent the same process causing the annular shadows seen in roentgenograms of the chest.

I wish to express my appreciation to Drs. Holman, Chandler and Cooley for the opportunity to study this material pathologically.

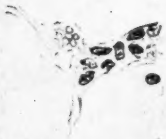
BIBLIOGRAPHY

(1) SABIN, F. R.: Cellular studies in tuberculosis, Amer. Rev. Tuberc., 1932, xxv, 153.
(2) SABIN, F. R.: Cellular reactions in tuberculosis, Tr. Nat. Tuberc. Assoc., 1931, p. 195.
(3) FRIED, B. M.: The histogenesis of the tubercle in the lung, Ibid., 1931, p. 218.
(4) VORWALD, A. J.: The early cellular reactions in the lungs of rabbits injected intravenously with human tubercle bacilli, Amer. Rev. Tuberc., 1932, xxv, 74.



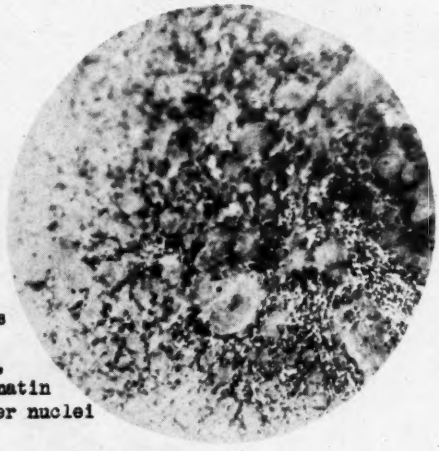
Large mononuclear cells both with and without protoplasm are present in interstitial tissue.

Six Hours after Tuberculous Embolus



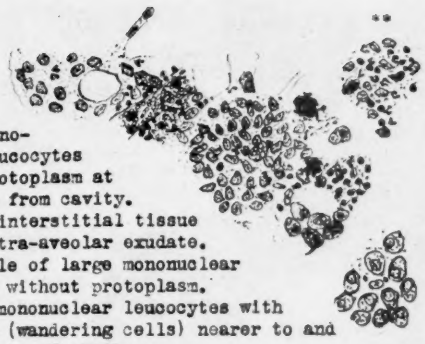
Mononuclear cells chiefly in alveolar walls.
Dilated and engorged blood vessels.

Twenty four Hours after Tuberculous Embolus.



In this marked hemorrhagic infarct there are red blood cells, small mononuclear cells with and without protoplasm, some that are slightly larger, in which the nuclei have chromatin granules, and then still larger nuclei typical of wandering cells.

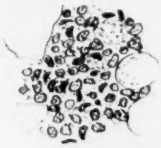
Twenty four Hours after Pyogenic Embolus.



P*
(1) Infiltration of mononuclear leucocytes without protoplasm at a distance from cavity. Thickened interstitial tissue without intra-aveolar exudate.
(2) Tubercle of large mononuclear leucocytes without protoplasm.
(3) Large mononuclear leucocytes with protoplasm (wandering cells) nearer to and in the debris of cavity.
In the walls of this cavity are polys, small mononuclear leucocytes and debris. Near this is a tubercle of wandering cells.

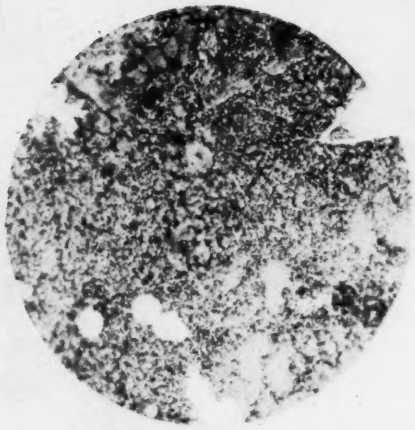
* Periphery ** Center

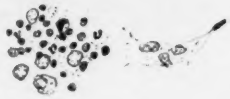
Five Days after Tuberculous Embolus



The cellular reaction here is very similar. Granular nuclei - small, medium and large - crowd the interstitial tissue and a few alveoli, but there is very little protoplasm present. Very few polys.

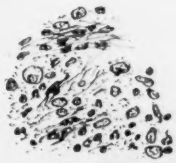
Pleural thickening is composed of possibly large mononuclear cells in large numbers and fibrils. Many new blood vessels. Few small round cells.



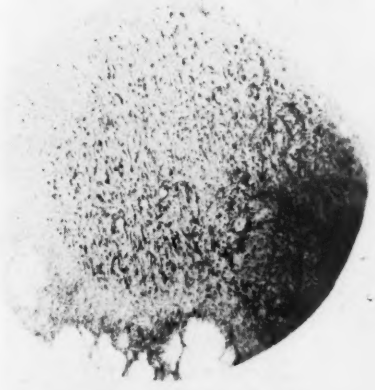


Interstitial tissue thickened with mononuclear leucocytes, hemorrhage into tissue and dilated blood vessels.
Necrosis with small round cells and leucocytes and large pale nuclei, probably wandering cells.

Seven Days after
Tuberculous Embolus

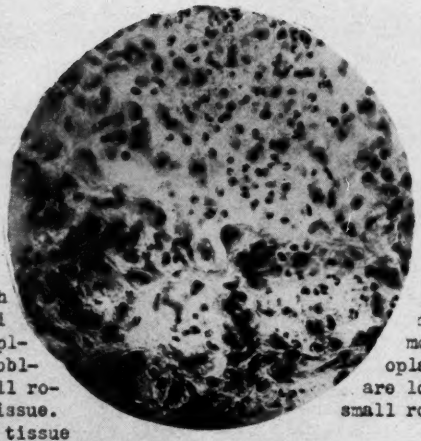


The wall of this large cavity contains polys on its inner surface, then nuclei of varying sizes. Some may be small lymphocytes (small round cells) and others all phases of activity of the large mononuclear. Rarely is one seen with any protoplasm. Some are associated with fibrous tissue formation.



**Four Days after
Pyogenic Embolus.
(Pleura)**

**Six Days after
Pyogenic Embolus.**



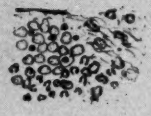
Definite area of necrosis but very thick interstitial walls, containing wandering cells with deep staining nuclei and branching protoplasm suggesting fibroblasts. Polys and small round cells in this tissue. Repair - connective tissue strands - growing in through necrosis. Nuclei resembling large mononuclears.

250x

Marked thickening of interstitial tissue with a small area of necrosis. The tissue is full of mononuclear cells, most of them with protoplasm. Many of nuclei are long and bent. Some small round cells.

Ten Days after Tuberculous Embolus.

Thirteen Days after Tuberculous Embolus.



In this large infarct there are many polys where tissue is entirely destroyed. Intermingled with this there are solid masses of large mononuclears without protoplasm, in whose nuclei the chromatin is arranged about the periphery only and stains very faintly. Occasionally a small mononuclear with protoplasm is seen.

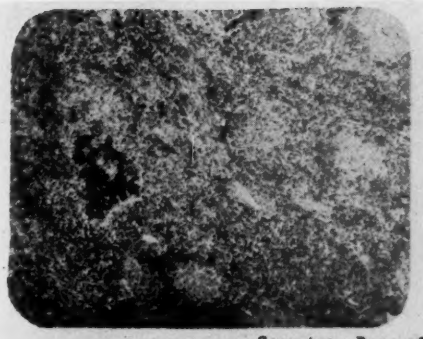
Process of destruction and repair are progressing rapidly. Polys are seen scattered through the tissue but the nuclei of the large mononuclears are larger and more chromatin is seen.

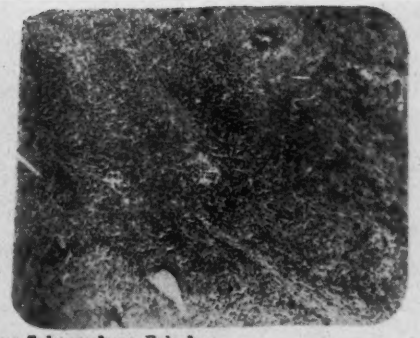
Fibrous tissue is well developed.

Eight Days after Pyogenic Embolus

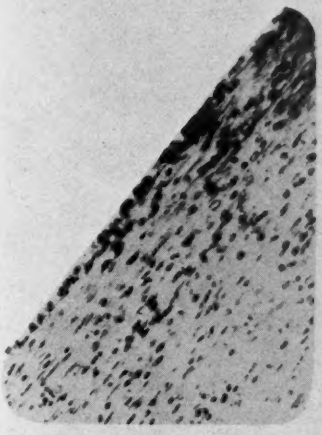
Cavity rupturing into Bronchus

Nine Days after Pyogenic Embolus.





Seventeen Days after Tuberculous Embolus.
Tubercles definitely marked off from surrounding Tissue.



Protoplasm of wandering cells is more vacuoled. These cells very numerous. Some have horseshoe nuclei. Small round cells present. No connective tissue.

Sixteen Days after Tuberculous Embolus

Mononuclear tubercle with nuclei irregular in shape - some round, some spindle. Then zones of small round cells and fibroblasts and fibrous tissue. Between the tubercles there is small round cell infiltration. Very few polys. Some small round cells in center.

Seventeen Days after Tuberculous Embolus

Still many polys in the wall of the cavity, but fibroblasts are very numerous and the nuclei well flattened. Beyond the cavity there are large mononuclears with well developed protoplasm. Several parts of the cavity wall are lined with cuboidal epithelium. (see photo)

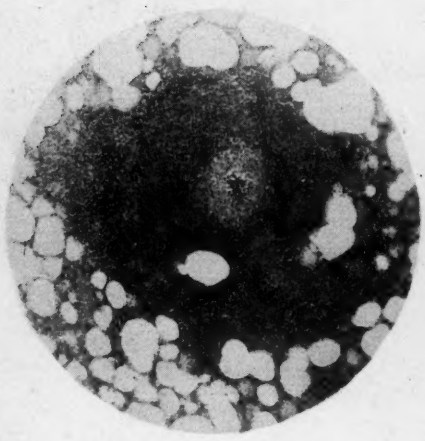
Thirteen Days after Pyogenic Embolus

While there is no cavity in this section, there are several polys; but the predominating cells are the large mononuclears with varying sized nuclei and protoplasm. Transition to fibroblastic state seen in the blood vessels. Dense, compact nuclei seen in the interstitial tissue.

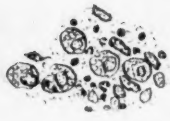
Sixteen Days after Pyogenic Embolus

Healing has progressed to such an extent that no polys are seen. The large mononuclears are loosely arranged on the inner aspect of the cavity. Loose fibrolastic tissue is superimposed and then dense connective tissue.

Twenty one Days after Pyogenic Embolus



Tubercle surrounded by Pneumonitis; caseating Tubercles.
Twenty three Days after Tuberculous Embolus.



In caseated areas leucocytes and small round cells predominate. Even there nuclei of wandering cells are seen. Elsewhere wandering cell protoplasm is markedly reticulated or full of vacuoles. Some attempt at repair is suggested by elongated nuclei.

Twenty five Days after
Tuberculous Embolus.

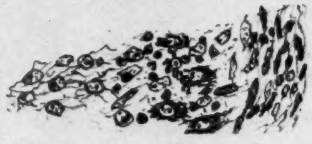
Tubercles in all stages of development - cellular, caseous and fibrous. Early connective tissue with oval nuclei and older fibrils with more condensed nuclei. Mononuclear cells with protoplasm crowd the surrounding area.

Thirty five Days after
Tuberculous Embolus.

This is not as advanced as in the preceding section but the reaction of polys to necrosis and developement of repair by large monos as possible fibroblasts is evident.

Thirty three Days after Pyogenic Embolus.

Cavity from center to periphery. Large mononuclears with oval shaped nuclei, most of them containing one nucleolus. Near the center of the cavity they possess fibrils. Then a zone of mononuclears and small round cells and polys. These merge into a fibrous wall with many nuclei - becoming flattened.



Fifty one Days after Tuberculous Embolus

Continued evidence of repair. Loosely arranged fibrous tissue - very vascular. Similarity of nuclei of wandering cells and fibroblasts.

Forty one Days after Tuberculous Embolus

Hemorrhagic infarct without much repair. In the inner zone polys and blood cells predominate. Further away many small and large mononuclears and with occasional fibroblasts; interstitial tissue shows many large mononuclears and polys. This shows a weak response.

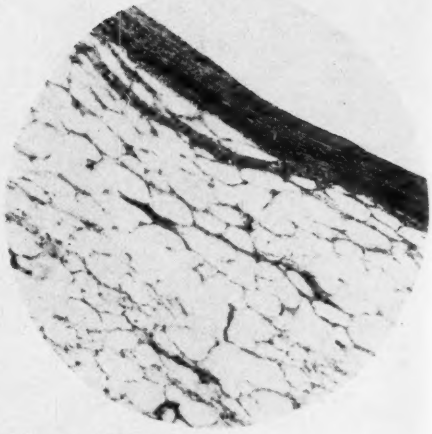
Dense fibrous wall with compact fibroblasts and in places a few oval nuclei of large mononuclear type.

Forty Days after Pyogenic Embolus

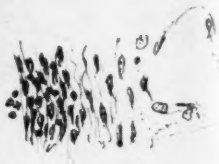
Sixty two Days after Pyogenic Embolus.

Cavity from center to periphery. All stages of mononuclear cell activity - oval nuclei with and without protoplasm as phagocytes; light staining elongated nuclei with thin fibrils; others, more mature, darker staining and heavier fibers; some very large cells with large bits of debrie, and one shell without nucleus. Tissue is vascular.

Ninety Days after
Tuberculous Embolus



Dense fibrous tissue lining cavity. Few small round cells scattered in patches, then layer of less dense fibrous tissue. Infiltration of interstitial tissue fades rather promptly at a short distance from the cavity wall.



Ninety two Days after
Tuberculous Embolus.

Very firm fibrous wall with a few faintly staining large mononuclei on the surface. Interstitial tissue shows no reaction.

Sixty three Days after Pyogenic Embolus.

TUBERCULOMA OF THE BRAIN

With a Report of 4 Cases[1]

ERNEST SCOTT AND GRANT O. GRAVES

The occurrence of four cases of cerebral tuberculomata in the autopsy service of the Pathological Department of Ohio State University within the past two years has aroused interest, and a review of the subject seems to warrant the report of these cases, together with an analysis of the literature bearing upon them. A complete review of the recorded cases as to incidence, location, age, sex, and distribution has been attempted, with a discussion of the more recent work on tuberculoma of the brain. The symptomatology, the pathological process, and the surgical treatment of the condition have recently been well presented by Anderson (1) and will not be discussed in this report.

LITERATURE

The earliest reported case of tuberculoma of the brain was that of Ford (2) in 1790 and recorded a solitary tuberculoma in the cerebellum of a child of nine years. An investigation of the literature reveals that 815 cases have been recorded since then.

The first collection of tuberculomata was made by Ogle (3) in 1864, consisting of 47 cases occurring at St. George's Hospital between 1841 and 1863. Ladame (4) in 1865 collected 109 cases. In 1881 Bernhardt (5) assembled a series which included 86 cases not assembled by Ladame and in the same year Steffen (6) published a series of brain tumors with 28 additional[2] cases of tuberculoma.

Hale White (7) reported 45 tuberculomata that had occurred at Guy's Hospital between 1872 and 1884. Starr (8) in 1889 reviewed the cases collected from the literature to the year 1888. This series however was limited to individuals under the age of 19 years. Later Starr (9) published a table of tumors in adults, including tuberculomata from "his own American experience, Bernhardt's collection (5), Bramwell's book

[1] From the Department of Pathology, Ohio State University, Columbus, Ohio.

[2] All mention of "number of cases," as stated in the within-cited collections, include only the cases that have not appeared in a list of an earlier author.

(10) and Bernhardt's digests in *Virchow's Jahresbericht* (1888–1892)." About the same time Seydel (11) reported 27 tuberculomata seen in the Pathological Institute of Munich. Raviart (12) in 1900 made a collection of 32 cases located in the cerebral peduncles. In 1904, Goublot (13) collected 37 additional tuberculomata and in 1909 Zappert (14) published a series of 61 tuberculomata of children from the Neurological

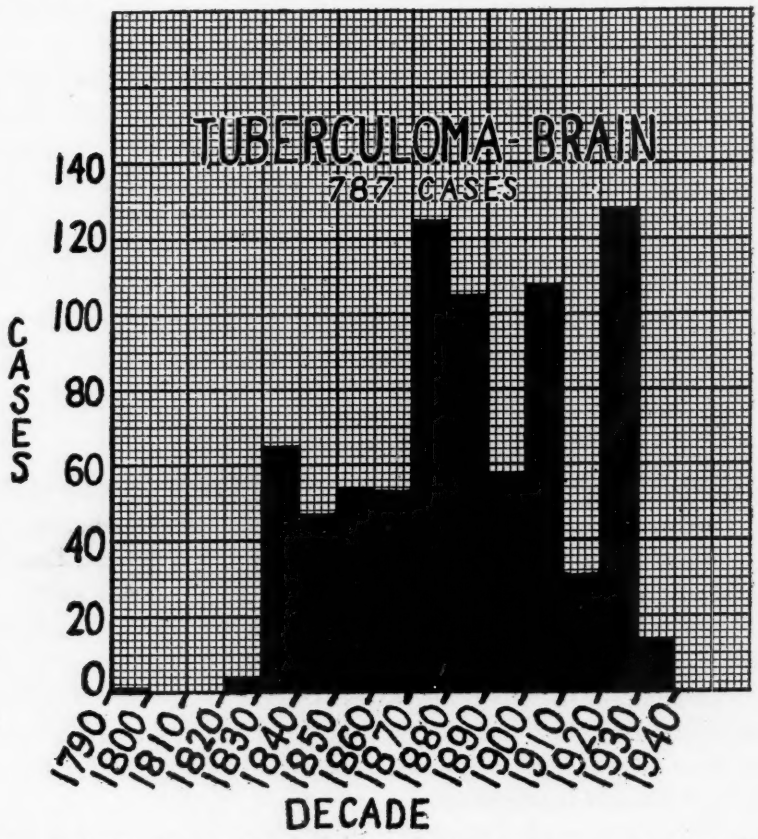


FIG. 1. Distribution of 815 cases from the literature according to decades. Increase since 1880.

Institute of the University of Vienna. The following year Valobra (15) made a collection of 18 tuberculomata of the mesencephalon. More recently, in 1928, Anderson (1) added a bibliography to the above lists, which included 102 cases. The next year Ferris (16) added 9 cases. In our own list (table 1) appear 129 cases not included in the above collections, bringing the total number of tuberculomata to 815.

Of these 815 cases, 787 (96 per cent) could be definitely placed chronologically, according to the time of their original publication (figure 1). This graph indicates little, however, except perhaps the activity of medical men reporting such cases. It would be unwise to interpret it as meaning that tuberculomata of the brain were increasing in the face of the decreasing general death-rate from tuberculosis.

In regard to the decade analysis of cases in the literature Van Wagenen stated earlier (17) that

> If the number of examples of a given disorder reported in the literature from decade to decade can be regarded as an index of the frequency of its occurrence, this phase of tuberculosis may be on the decline. Either interest in the subject has waned, or, what seems more probable in view of the drop in the incidence of tuberculosis in general, tuberculomas of the brain in this country at least have become comparatively rare.

This statement does not seem to be substantiated from our analysis of the literature.

Report of Cases

Case 1.—Occipital decompression in an adult. Death in nine hours. Necropsy disclosed a cerebellar tuberculoma. *History:* The patient, H. J., a colored male, aged 37 years, was admitted to the University Hospital on January 30, 1930. There were no operations or traumata in his history. Seven months before admission headaches began and became progressively more severe. The immediate complaint was severe pain on the right side of the head. *Examination:* There was severe pain on head motion with some tenderness on palpation of the right temporal region. The neck showed rigidity with some tenderness over the cervical vertebrae. There were bilateral choked discs with sluggish reactions to light, the right pupil slightly larger than the left. There was deviation of the tongue to the right, a weaker left handgrip, and the cremasteric reflex was obtained on the right but not on the left side. The patellar reflexes were diminished. Blood and spinal Wassermanns were negative, and the urine and the blood counts normal. The blood-pressure was normal. Spinal fluid on the day of admittance was clear and under increased pressure (18 mm.). Ventriculography at this time showed no pathological changes. Six days later the pressure was 30 mm. On the day of the operation the roentgenogram showed a marked enlargement of the left ventricle.

Operation: On February 12, 1930, a right occipital decompression was performed. No tumor mass was encountered. Four hours after the operation,

TABLE 1

Case reports from the literature

DATE	AUTHOR	SEX	AGE	LOCATION
			yrs.	
1844	Louis, P. C. A. (Researches on phthisis, Sydenham Soc., London, ed. 2)	F.	19	2 occipital thalamus cerebellum 2 cerebrum
		M.	24	medulla
1871*	Lancereaux and Lackerbauer (Atlas d'anat. path., Paris, 1871, p. 395)	F.	65	thalamus
1887	Horsley (Brit. M. J., i, 863–865)	M.	18	cerebellum
		M.	20	paracentral
	May (Lancet, April 16, 1887)	M.	7	cerebellum
			mos.	
1890	Boltz, R. O. (Inaugur. Dissert., Kiel, 1890, p. 21)		5	
			9	
			yrs.	
			1	
			1	
			2	
			2	
	"Female mortality slightly greater than male"		2	9 cerebrum and 9 cerebellum
			2	
			3	
			3	
			3	
			4	
			4	
			3 5–10	
			2 10–15	
1893	Booth and Curtis (Annal. Surg., February, 1893)	M.	24	frontal
	Dunlop, G. H. M. (Edin. Hosp. Reps., i, 298–302)	M.	5	cerebellum
		M.	6	pons
		M.	7	frontal
		F.	8	cerebellum
			?	cerebellum
			?	cerebellum
			?	cerebellum
			?	cerebrum
			?	cerebrum
			?	pons
	Siemon* (Inaugur. Dissert., Marburg, 1893)		?	frontal

* Calcified tuberculomata.

TABLE 1—*Continued*

DATE	AUTHOR	SEX	AGE	LOCATION
			yrs.	
1894	Beck, B. (Beitr. z. klin. Chir., 1894, xii, 1–142)		7	solitary tumors
1903	Foa, P.* (Giorn. della R. Accad. di Med. di Torino, 4th series, ix, 403)	M.	10	cerebellum
1907	Redlich, E. (Arbeit. a.d. Neurol. Inst. a.d. Wien. Univer., xv, 320–338, case 4)	F.	24	multiple
1908	Bruns (Die Geschwülste des Nervensystems, Berlin, ed. 2, S. Karger, 1908)		?	paracentral
			?	paracentral
			?	cerebellum
			?	cerebellum
			?	cerebellum
			?	cerebellum
			?	cerebellum
			?	pons
			?	medulla
			?	base
1909	Klienebergers** (Fortschr. a.d. Geb. d. Röntgenstrählen, xiv, p. 100)	M.	12	corpus callosum
	Sabat** (Verhandl. IX Kongresses der Deutsch. Röntgenges.)		17	cerebrum
1910	Wosnjessensky (Chirurgie-russ., 1910, xxvii, no. 162, 1910)		?	paracentral
1912	Tooth, H. H. (Brain, 1912, xxxv, 61)		14	tuberculomata
1916	Clarke (Rev. Neurol. and Psych., xiv, 485)		?	paracentral
			?	paracentral
			?	cerebellum
			2?	pons and medulla
	Corsica (Pediatria, Napoli, 1916, xxiv, 660–666)	F.	5	multiple cerebrum
	Heuer and Dandy (Bull. Johns Hopkins Hosp., 1916, xxvii, 224)		?	frontal
			?	midbrain
1917	Acuna and Sanchez (Semana Medica, 1917, xxiv, 762)	M.	1½	cerebellum
	d'Espine and Demole (Arch. Méd. Enf., 1917, xx, 355)	M.	7	2 in pons
1919	Sacco and Ruiz (Sem. Med., 1919, xxvi, 348)		?	cerebellum

** Calcified tuberculomata diagnosed by roentgenogram.

TABLE 1—*Continued*

DATE	AUTHOR	SEX	AGE	LOCATION
			mos.	
1920	Bazan (Sem. Med., 1920, xxvii, 797–800)	F.	17	cerebellum
			yrs.	
	Marie, DeMartel and Behague* (Revue Neurologique, xxvii, 1109)	M.	18	frontal
	Strom** (Fortschr. der Röntgenstr., xxvii, 596–599)	F.	21	frontal
1921	Allende and Martini (Rev. Assoc. med. Argent., Buenos Aires, 1921, xxxiv, 48–68)	M.	23	cerebellum
	Drebschok, F., (Wien. klin. Wchnschr., xxxiv, 603–604)	F.	42	pons cerebellum multiple cerebrum
	Frazier, C.*** (Tr. Am. Neurol. Assoc., 1921, p. 122)	M.	26	central motor (survived operation 22 months)
	Marburg and Ranzi (Arch. f. klin. Chir., 1921, cxvi, 96–161)		? ? ? ? ?	cerebrum paracentral cerebellum cerebellum cerebellum
	Randolph, B. M. (Amer. Rev. Tuberc., 1921, v, 665–669)	M.	34	frontal
1922	Alvarez, B. G. (Arch. espan. Pediat., 1922, vi, 513–516)	F.	2½	cerebral peduncle
	DeMartel and Bouttier (Rev. Neurologique, xxix, 583)	F.	10	cerebellum
	McClelland (J. Mich. Med. Soc., xxi, 15)	F.	25	multiple in cerebellum and thalamus
	Stenvers, H. W. (Schweiz. Arch. Neur. u. Psych., 1922, xi, 221–229)	M.	40	medulla
			mos.	
1923	Bortagaray, M. H. (Sem. Med., xxx, 1225–1230)	M.	15	pons cerebellum
			yrs.	
1924	Kingreen (Fortschr. d. Röntgenstr., xxxii, p. 55)	M.	10	cerebrum
1925	Ardin-Delteil and Levi-Valensi (Rev. Neurol., Par., ii, 464–473)	F.	30	pons

*** Cases of tuberculomata surviving operation over 4 years.

TABLE 1—*Continued*

DATE	AUTHOR	SEX	AGE	LOCATION
			yrs.	
1925	Tomasi (Policlinico, 1925, xxxii, 277–279)	M.	22	cerebellum
1926	Dimitri (Sociedad de Neurologia y Psiquiatria, Winter Sess., July 30, 1926)	M.	?	pons
	Nobecourt, Paraf & Veil*** (Bull. Soc. de Pediat. de Paris, 1926, xxiv, 326)		10	cerebellum (living 4 years after operation)
1927	Carnot, Variety and Guedon (Bull. et Mem. Soc. Méd. d. Hop. de Paris, 1926, xxiv, 326)	M.	20	thalamus
		M.	28	thalamus
	Dowling (Rev. oto-neur-oftal., i, 78)	M.	17	frontal
		F.	18	parietal
		F.	38	cerebellum
	Furui, R. (Arb. a.d. neurol. Inst., a.d. Wien. Univ., xxix, 248–264)	M.	10	cerebellum
		F.	5	cerebellum
			?	cerebellum
			?	cerebellum
			?	cerebellum
			?	cerebellum
			mos.	
	Pitfield, R. L. (Arch. Pediat., 1927, xliv, 502–507)	M.	19	medulla
			yrs.	
	Smith (J. Path. & Bact., xxx, 583)	F.	62	cerebellum
	Stewart* (J. Path. & Bact., xxx, 577)	M.	27	cerebellum
		M.	17	cerebellum
	Wolbach (cited by Van Wagenen, Arch. Neur. & Psych., xvii, 58)			9 tuberculomata in children under 12 years
1928	Caussade, Cornil & Girard (Rev. Neurol., i, 83)	M.	3	corpus quadratum
	Dowman and Smith (Arch. Neur. & Psych., xx, 1312–1329)	M.	under 10	cerebellum
	Grinker and Lifvendahl (Arch. Neur. & Psych., xx, 415–416)		4 mos. to 63 yrs.	3 cerebellum
				1 pons
			⅔ under 19 yrs.	17 cerebrum
				(of 21 cases 4 were multiple)
			yrs.	
	Schroth, I. H. (J. Med. Cinc. 1928, ix, 485–487)	M.	38	temporal
	Sepich, M. J. (Rev. Assoc. Med. Argent., xli, 515–560)	M.	47	cerebellum

TABLE 1—*Concluded*

DATE	AUTHOR	SEX	AGE	LOCATION
			yrs.	
1928	Stone, T. T. (Arch. Neur. & Psych., xx, 415–416)	F.	38	cerebellum
		F.	44	cerebellum
1929	Charlone (Arch. Lat.-Amer. de Pediat., xxiii, 539–546)	M.	4	multiple in cerebrum
	Gleich and Sala (N. Y. State J. Med., xxix, 81)	F.	3	cerebrum
	Kwan, S. T.*** (Arch. Neur. & Psych., xxii, 1093–1094)	M.	5	cerebellum (living 12 years after operation by Dr. Chas. Frazier)
	Roger, Bremond and Simeon (Rev. d'oto-neuro-ophthal. Par., vii, 26–31)	M.	22	cerebellum
	Schidlowsky (Arch. f. klin. Chir., clv, 703–710)	F.	2	parietal
		F.	14	frontal
		F.	22	cerebellum
		M.	24	cerebellum
		M.	26	frontal
		M.	34	internal capsule
		M.	36	pons
		M.	38	caudate nucleus
		F.	43	multiple in cerebellum and medulla
1930	Gorter, E. (Ztschr. f. Tuberk., lv, 414–418)	M.	12	lateral ventricle
	Jacarelli (Policlinico, Rome, 1930, xxxvii, 434)	M.	32	cerebellum
	Manolesco, D., and Lazaresko, D. (Rev. d'oto-neuro-ophth., 1930, viii, 382)	M.	19	lenticular nucleus
	Moore (Arch. Neur. & Psych., 1930, xxiii, 795–797)	F.	5	5 in cerebrum cerebellum
	Paterson and Stevenson (Glascow Med. Journ., 1930, vi, 281–290)	M.	16	occipital
1931	Germer (Ugeskrift for Laeger, Copenhagen, xciii, 6–26)	F.	12	paracentral
	Hardy, F. (Mich. State Med. Soc. Journ., 1931, xxx, 372)	F.	9	cerebellum
	Scott and Graves	M.	3	cerebellum
		M.	20	pons
		F.	25	cerebellum
		M.	37	cerebellum

the pulse, respiration and temperature began to rise. The patient died nine hours after the operation.

Necropsy: The postmortem was restricted to the head. The dura was tightly stretched over the entire brain surface. The convolutions were flattened and compact. The right cerebellar fossa was seen to be larger and deeper than the left and covered by the remains of adhesions. The bone of these fossae was very thin. Cut-sections of the brain revealed enlargement of both ventricles and a tumor mass (3 x 5 cm.) in the posterior part of the right cerebellar hemisphere, which was hard, firm and adherent to the dura. The mass was not encapsulated. Microscopic sections proved the tumor to be a tuberculoma.

Case 2: A left cerebellar tuberculoma with spinal meningitis in a child aged three and one-half years, disclosed at necropsy. *History:* The patient, E. D., a colored male, aged 3½ years, was admitted to the Children's Hospital on June 6, 1930. A history was given of measles and whooping-cough but no tuberculosis. A severe fall from an ice-wagon took place some weeks before the first illness, which occurred on May 29, 1930. At this time he would not eat and did not want to play, although there were no specific complaints. On May 31 the patient had a high fever but no chills or convulsions. No diagnosis was made at that time. On June 4, a second physician was called, who found only a sore throat with no elevation of temperature. Soon the patient began to vomit and continued to do so for several days. *Examination:* On the day of admittance, the boy was in a semicomatose condition from which he was easily aroused. There was headache, opisthotonos, positive Kernig's sign, positive Brudzinski's sign, hyperactive patellar, biceps and triceps reflexes, pupils unequal and sluggishly reacting to light, tongue coated and dry, throat reddened and with purulent discharge on the posterior pharynx. The cervical lymph nodes were palpable. The chest and heart were negative. Movement of the head and legs apparently caused considerable discomfort. Spinal puncture made on admission gave a clear fluid under increased pressure, which later became bloody. Laboratory findings due to the blood were negative on the first two spinal punctures. The third spinal puncture on June 11 gave a clear fluid with a total count of 1,380 cells with 42 per cent lymphocytes, negative sugar, slight increase of globulin and no microörganisms. The blood count was 5,700,000 reds, 16,700 whites with 76 per cent polymorphonuclears, and haemoglobin was 88 per cent.

Course: During hospitalization the temperature rose from 99° to 105°. After admittance the rigidity became greater with some spasmodic twitching of the extremities. On June 12 the rigidity became less and remained so until death on June 15, two weeks after the onset of symptoms.

Necropsy: The postmortem examination revealed a tuberculous cavity of

the upper lobe of the right lung with adhesions, and tuberculous mediastinal and bronchial lymph nodes. In the examination of the head, the dura was found tightly stretched over the brain, which was swollen and oedematous. The sulci in places were filled with purulent exudate. On removing the brain, an exudate was found around the optic chiasm, crura and infundibulum. The cerebellum on the left side was torn on removal, due to adhesions to the dura. A small hydro-cyst (1 cm. in diameter) was located between the cerebellar hemispheres. The right cerebellar hemisphere was indented by the swollen left one. On cut-section the brain disclosed a light-colored tumor mass (3 x 5 cm.) involving the whole of the left cerebellar lobe except a small lateral margin, a bilateral hydrocephalus with clear fluid, large foramina of Munro, a swollen aqueduct cerebri and a gelatinous exudate on the inferior surface of the pons and medulla. Microscopic sections of this tumor indicated its tuberculous nature.

Case 3: A left pontile tuberculoma in a man aged twenty years, disclosed at necropsy. *History:* The patient, S. R., a colored male, aged 20 years, was admitted to the Franklin County Tuberculosis Sanatorium on April 1, 1930. He was admitted with active tuberculosis of the lungs, complaining of headache and pain in the back, with chills, profuse diaphoresis, weakness, restlessness and watery stools. *Examination:* The patient was very nervous and delirious at times. On admission there were no abnormal neurological findings. The patient presented the picture of extensive tuberculous pulmonary involvement. The blood Wassermann showed a 4 plus and the Kahn a 3 plus. The spinal fluid was not under increased pressure.

Course: Early the delirium became worse. However, after a thoracentisis the temperature and mental condition became normal. In October, 1930, his abdomen became distended. At this time there was an internal divergence of the left eye. There was a partial hemiplegia and anaesthesia of the right side. The abdominal and cremasteric reflexes on the right side were absent and the Kernig's and Babinski of this side were positive. In the last two months, the patient showed a complete right-sided paralysis. Three weeks before his death the back of the neck became stiff and painful. A projectile type of vomiting was frequently seen thereafter, in addition to an incontinence of urine and faeces. In the last two weeks the patient became delirious. Death followed on January 23, 1931.

Necropsy: The autopsy examination revealed a tuberculoma of the pons on the left side, oedema of the pons and left crus, a tuberculous empyema of the right chest, tuberculous peritonitis, nodular tuberculosis of the liver and spleen, and general involvement of the mediastinal, mesenteric, retropleural and retroperitoneal lymph nodes. The dura was tense and thickened. The brain was slightly larger than normal and with narrow sulci and flattened convolutions,

more apparent on the right side. The right temporal and occipital regions were large and soft. At the base of the brain the vessels were normal. The left pons was unusually large. The upper part of the medulla was slightly swollen. On cut-section, the pons revealed a tuberculoma (3.5 cm. in diameter), with a reddish-brown border about a central caseous mass. The lateral hemispheres contained dilated ventricles with an increased amount of clear fluid with no evidence of infection.

Case 4: A right cerebellar tuberculoma in a woman twenty-five years of age, six months pregnant, disclosed at necropsy. *History:* The patient, A. P., a white female, aged 25 years, was admitted to the University Hospital on February 2, 1931, on the obstetrical service, she being six months pregnant. Past history showed the patient to have had 5 previous pregnancies, the first two premature at six months, the last three normal spontaneous labors. The previous pregnancies were accompanied only by the usual vomiting in the first trimester. When the patient was four and one-half months pregnant she commenced vomiting a greenish watery substance and this condition grew worse until two weeks before death, when she was forced to bed. The patient in the hospital vomited everything taken except a little water, the vomiting being worse in the morning. During the last month there had been severe frontal headaches, referred to the occiput. *Examination:* On the day of admittance, the patient did not show any abnormal findings by systems. The admission blood-pressure was 116 systolic, 65 diastolic. Blood findings were negative and there was a negative Wassermann.

Course: The patient remained in the hospital seven days. During this time the vomiting and headache grew worse. The headache was constant and usually frontal. The patient on the last day fell asleep and four hours later died.

Necropsy: The postmortem examination revealed a tumor of the right lobe of the cerebellum and internal hydrocephalus, in addition to chronic adhesive pleuritis, chronic caseous tuberculosis at the apex of the left lung, splenomegalia, chronic nephritis, nephroptosis of the left kidney, hydronephrosis of the right kidney and ureter, goitre, lactating breasts, and advanced pregnancy.

Examination of the brain showed considerable distention. The convolutions were flattened and the sulci practically obliterated. No increase of fluid was observed in the subarachnoid space. The lateral ventricles were moderately distended with a clear fluid. The tentorium was tense. The cerebellum was soft, and the pons and portions of the cord were removed with some difficulty, apparently due to the swelling of the cerebellum. On removal of the cerebellum a portion was jammed into the foramen magnum which left its imprint on the cerebellum. Incision through the cerebellum revealed an asymmetrical condition, an enlargement on the right side, which proved to be a tuberculoma.

INCIDENCE

Table 2 shows the frequency of appearance of tuberculomata in the autopsy records of the various countries. It may be seen from the table

TABLE 2

Autopsy incidence

AUTHOR—YEAR—PLACE	NUMBER OF AUTOPSIES	AUTOPSY, PER CENT	NUMBER OF TUBERCULOMATA	TUMOR, PER CENT	NUMBER OF BRAIN TUMORS
England					
Stewart (18): Leeds Infirmary	1,000	1.2	12		
Tooth (19): 1912–1913			14	2.8	500
White (7): 1884: Guy's Hospital	5,850	0.7	45	45.0	100
Germany					
Beck (20): 1869–1894: Pathological Institute of Heidelberg	6,177	0.01	1	2.5	50
Boltz (21): 1890: Pathological Institute of Vienna	2,638	0.6	18		
Marburg and Ranzi (22): 1901–1919: Eiselsberg's Clinic			5	1.5	318
Seydel (11): 1892: Pathological Institute of Munich	8,488	0.3	27	27.0	100
Russia					
Schidlowsky (23): 1912–1927: Alexanderkrankenhausen	7,744	0.03	2	3.3	60
Leningrad	3,883	0.2	8	17.0	47
United States					
Anderson (1): 1928: Philadelphia General Hospital	1,768 brains examined: 27 tuberculomata				
Clarke (24): 1916: University of Pennsylvania.			6	6.0	99
Dowman & Smith (25): 1928: Piedmont Hospital			1	1.0	100
Ferris (16): 1929: New Haven Hospital	1,699	0.4	8		
Schroth (26): 1921–1928: Cincinnati	900	0.2	2		
Van Wagenen (17): 1925: Peter Bent Brigham Hospital			14	1.4	1,000
Scott and Graves: 1907–1931: Ohio State University	3,853	0.1	4	19.0	21

that the autopsy incidence of tuberculomata is extremely variable,—anywhere from 1.2 per cent at the Leeds Infirmary (18) to 0.01 per cent

at the Pathological Institute of Heidelberg (20), with an average of 0.39 per cent. This average seems to us very high, for in those countries in which the number of autopsies per population is high the percentage is much lower. In Germany Beck (20) found in 6,177 autopsies at the Pathological Institute of Heidelberg over a 25-year period a 0.01 per cent occurrence of tuberculomata, while in Russia Schidlowsky (23) found

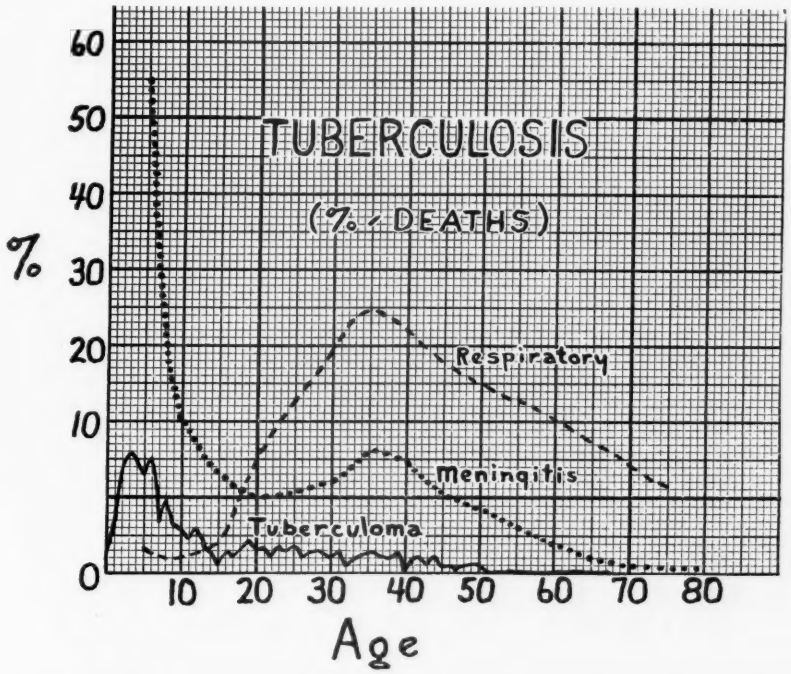


FIG. 2. Graph of the percentages of deaths due to various forms of tuberculosis at different age-periods. Brain tuberculoma curve based on 646 cases from the literature. Other curves from figures of the tuberculous deaths in the U. S. Registration Area for 1927.

in 7,744 autopsies over a 15-year period at the Alexanderkrankenhausen a 0.03 per cent occurrence.

When the incidence of tuberculomata among brain tumors is considered, however, the majority of percentage incidences are found to vary from 3.3 to 1.4 with extremes as high as 45 per cent (Guy's Hospital). The average is 2.5 per cent, which corresponds closely to Beck's and Schidlowsky's figures (in Germany and Russia, respectively), which were derived from large autopsy services.

AGE

Tuberculoma of the brain by our analysis is far more common in children than in adults. Of the 646 cases in which age was mentioned 49.5 per cent were found before the age of ten years. In the decades between the ages of 10 and 40 years the number is very nearly constant, averaging 9 per cent. Beyond this age it rapidly dwindles, to entirely disappear by the age of 68. Figure 2 indicates the relative percentages

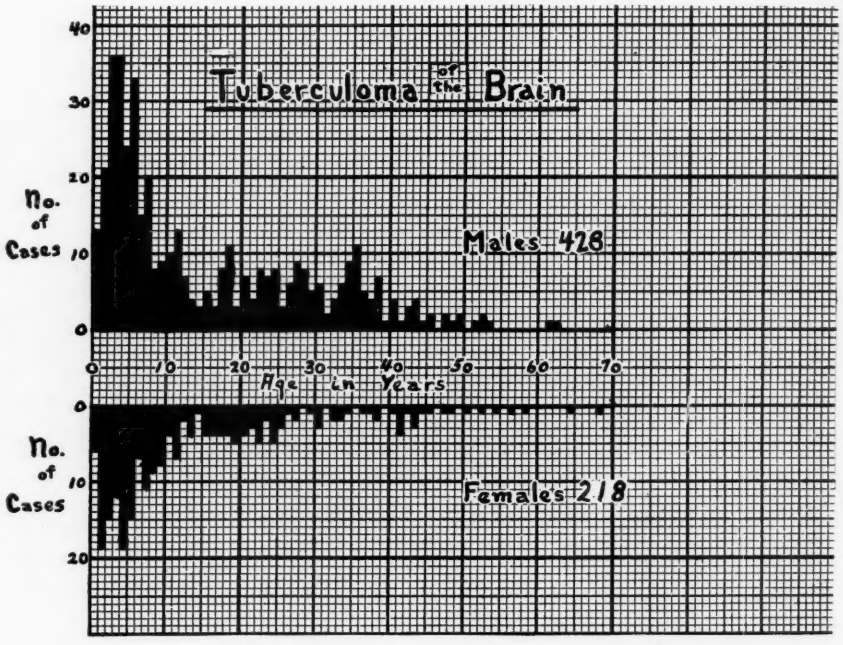


FIG. 3. Chart of the sex distribution according to age of 646 cases of tuberculoma of the brain from the literature.

of deaths at the different age-groups of 646 cases of tuberculomata with a comparison of the meningeal- and respiratory-system forms of tuberculosis in the U. S. Registration Area for 1927.

These comparisons suggest that common factors are present in meningeal and tuberculomatous involvements of the brain (see *Discussion*, p. 188).

Figure 3 also shows in graphic form the age distribution of the two sexes and again indicates that the majority of infections occur in the first decade of life.

SEX

In table 3 we find 66 per cent of the cases to be males and 34 per cent to be females, or a ratio of 2 to 1. These figures are slightly different from those of Anderson (1) who states, "Males constitute twenty-one of the list (77.7 per cent), with only six females (23.3 per cent)."

The percentage of females is relatively greater in the earlier years of life, showing an increased frequency before the age of fourteen years. This disparity between the incidence in the two sexes is more markedly indicated in the general death-rate from tuberculosis. Although many causes have been proposed, the truth is not known.

TABLE 3

Age and sex analysis of brain tuberculomata (646 cases from the literature)

AGE-GROUP	MALE CASES	PER CENT	FEMALE CASES	PER CENT	BOTH SEXES CASES	PER CENT
yrs.						
Under 5	107	25.0	52	23.8	159	24.5
5–9	100	23.3	62	28.3	162	25.0
10–14	43	10.0	24	11.1	67	10.4
15–19	30	7.0	17	7.8	47	7.3
20–24	30	7.0	19	8.8	49	7.5
25–34	58	13.5	19	8.8	77	11.9
35–44	47	10.8	15	7.6	62	9.3
45–54	15	3.4	5	2.3	20	3.1
55–65	2	0.4	3	1.4	5	0.8
65–74	0	0	1	0.5	1	0.2
75–	0	0	0	0	0	0
Total.....	428	66.0	218	34.0	646	100.0

LOCATION

Most discussion and difficulty of analysis has been in regard to the location of the tuberculomata. In this study we were able to gather 475 cases of solitary tuberculomata and 254 cases of multiple tuberculomata. Their location is shown in figure 4.

Explanation of the graph (figure 4) seems necessary to avoid misinterpretation. Whenever a case of multiple tuberculoma was considered, each site was recorded. Thus, if there were two in the frontal region and one in the frontal region of the other hemisphere the number three was scored in the frontal column. The black represents solitary tumors, the dotted area the definitely localized multiple sites and the clear areas with

the peaked tops the multiple-site occurrences of indefinite number. The height of the side walls of each clear column indicates the number of citations of indefinite numbers ("many tubercles"), so that these columns may extend upward indefinitely. The heights, however, indicate the relative possibilities of indefinite extent.

The following generalizations may be suggested: The frequency of occurrence of solitary tuberculomata in the total cerebrum is almost equal to that in the cerebellum. When solitary and multiple tuberculo-

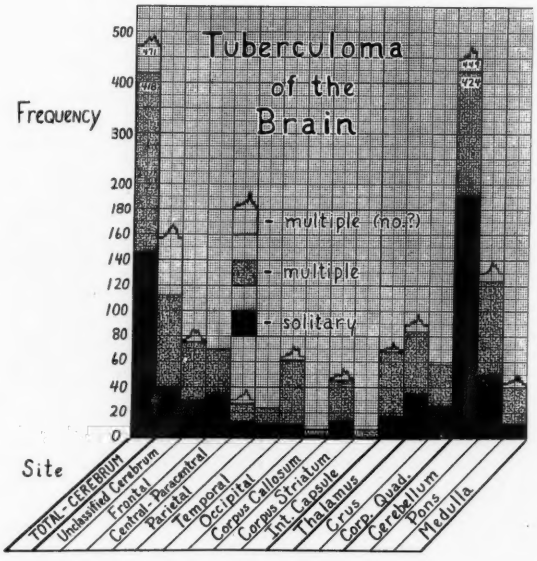


FIG. 4. Chart of the location occurrences of 729 cases of tuberculoma of the brain. Solid black indicates solitary tumors, dotted area indicates multiple-tumor-site occurrences and the clear peaked areas indicate multiple tumors of indefinite number of occurrences at the various brain regions.

mata are taken together (figure 4) the order of occurrence would seem to be cerebellum, pons, crus cerebri, frontal, central and paracentral, thalamus, occipital, corpora quadrigemina, corpus striatum, medulla, parietal, temporal, internal capsule and corpus callosum. The frontal, central and occipital regions of the cerebrum seem to be more frequently affected than the other parts with perhaps the exception of the corpus striatum. The internal capsule and the corpus callosum seem to be rarely affected by tuberculous infection. No recorded cases of tuberculoma of the hypophysis were found in the literature.

Although not a part of our analysis, the general consensus of opinion is that there is little predilection for one side of the brain over the other. It would seem that the location was determined by chance, the blood-vessel channel possibilities of both sides being equally good.

NUMBER OF TUMORS

Already it has been mentioned that solitary tuberculomata are about twice as frequent as the multiple ones, 475, or 65 per cent, to 254, or 35 per cent. Anderson (1) in a limited number of cases puts the number of solitary tuberculomata at 75 per cent.

TABLE 4

Multiple tuberculoma cases

NUMBER OF TUMORS	CASES	PER CENT
2	101	39.8
3	46	18.1
4	14	5.4
5	10	3.9
6	6	2.3
7	1	0.5
8	1	0.5
11	1	0.5
14	1	0.5
17	1	0.5
21	1	0.5
Indefinite	70	27.5
Total	254	100.0

Of the multiple tuberculomata those with only two sites are in abundance. Table 4 gives the number of cases and percentages of each "number of tumors" in a single brain. It is interesting to note the relative infrequency of high numbers of tumors in one brain. It is predominantly two or three. One case of 21 was recorded and one of complete involvement of one hemisphere. The term "indefinite" is used to indicate cases in which there was stated to be "many tubercles" in the brain. These indefinite cases represent one-fourth of all multiple involvements. This may perhaps change the above percentages somewhat but they will still represent much truth.

The relative distribution of multiple tuberculomata as to age and sex is similar to that of the single and multiple considered together (see pp. 184–185).

CALCIFICATION

Tuberculomata become calcified very rarely. In the 815 collected cases 11, or 0.01 per cent, were reported to be definitely calcified. Ogle (3) reported two cases of calcified tuberculoma, one in the occipital region of a 25-year-old male, the other in the cerebellum of a child. The remaining 9 cases are starred in table 1. Those with the double stars represent the cases diagnosed by roentgenogram. The cerebellum was the site in 4 cases, the frontal lobe in 3 and the cerebrum, corpus callosum, occipital lobe and thalamus, each in one case. All of the cases with the exception of one (65 years) occurred before the age of 27 years.

DISCUSSION

The origin of tuberculomata of the brain is by way of the blood-stream from some primary focus of infection. Rarely if ever is a tuberculoma of the brain found without other lesions in the body. A consideration of the locations of the different cases of tuberculoma indicates that no particular part of the brain is exempt and that a few areas are frequently attacked, namely the cerebellum and pons, the frontal, the central and paracentral, the occipital and corpus striatum. These areas are those which receive the majority of the infected blood first, in addition to being those areas supplied predominantly by the vertebral arteries. The other areas are at or nearer the end of the arterial streams and consequently are not the first possibilities for the lodging of the tubercle bacilli. Besides this anatomical predisposition there may be a varied tissue sensitivity. Knowing that the lipoid fraction of the tubercle bacilli is responsible for the tubercle-formation (27), the problem suggests itself of whether the injection of this material into various parts of the brain would indicate any specificity of different parts.

Considering the tubercle bacilli which cause the tuberculomata, we find nowhere in the literature any mention of the bacteriological nature of the microörganisms found within them. Are the tuberculomata caused by the long, deeply-staining bacilli, which are the less virulent, or by the short, faintly-staining ones, which are the more virulent, or perhaps by both types? And is there any relation between the bacteriological type and the number of tuberculomata in one brain? In answer to the first question, the work of Rich and McCordock (28) seems to be in point, in which they state that "we are unable to detect any difference in the fundamental tissue reaction of the body to different tubercle bacilli,

whether of high or low virulence, whether of types to which the body in question is resistant or is susceptible. . . . ."

Since the tuberculomatous growths are haematogenous, one may wonder why in cases of large tuberculomata of the brain there are so few concomitant meningitides. Both the brain substance and the meninges are well supplied vascularly. In fact both are subject to tubercle-formation, but meningitis does not result directly from the blood-stream infection. Through the experimental work of Rich and McCordock (28) in the production of tuberculous meningitis in rabbits and guinea pigs the answer is forthcoming. They state,

> Certainly, the factors of high allergy plus the presence of abundant circulating bacilli are not sufficient in themselves to bring about exudative tuberculous meningitis in rabbits and guinea pigs. We have however, in common with several investigators, regularly produced quite typical exudative meningitis in these animals by injecting tubercle bacilli directly into the subarachnoid space.

And then of the relation of tuberculomata to meningitis, they state,

> we have, then, in these caseous foci in the substance of the brain, a potential source of discharge of bacilli directly into the subarachnoid space. It is necessary only that, in their growth, they reach the meninges without encapsulation, or else discharge into the ventricular system; and this is exactly what we have found in 33 of the 40 cases of meningitis which we have studied (31 via the cortex, 2 via the ventricles). These tubercles within the brain substance do not, however, exhaust the possibilities of direct meningeal infection.

Their experimental work also explains why the operative removal procedures are in the majority of cases so futile. Most cases of tuberculoma of the brain sooner or later end in a meningitis, which is usually the cause of death. The only exceptions appear to be those patients whose tuberculomata have calcified or those who after operation did not develop a meningitis for some unknown reason. Perhaps the electrocautery, with its sealing effect, will offer a solution to the prevention of infection of the meninges.

Why is it that there is a greater mortality among the first decade of life in comparison to the later years? So far as is known, there is no inherent difference between the normal bodies of children and of adults which might account for the observed differences in reaction to the bacillus. Rich and McCordock (28) have expressed it well, which is, in brief, lack of resistance and allergy.

In the field of treatment most attention should be directed toward the relief of the general tuberculosis. Specific treatment for the tuberculoma is only in the experimental stage. Several lines of attack are being followed at the present time. There may be the possibility of ossification of the tuberculomata. Calcium, phosphorus and viosterol suggest themselves as possibilities of medication. The few cases of calcified tuberculomata indicate such a possibility. Whether there would be an ossification of the brain lesions before the visceral lesions and whether the lesions would be particularly selected for calcification, must await experiment. Kaminsky and Davidson (29) in a recent article on the effect of viosterol on calcification in pulmonary tuberculosis state:

> It will be noted that the positive results obtained in experimental tuberculosis, as cited above (Spies, Levaditi and Yuan Po, and Policard, Paupert-Ravault and Barral) followed the administration of either toxic or comparatively large nontoxic doses of irradiated ergosterol. The dosage of this drug, when applied to the study of human tuberculosis, must for obvious reasons be kept within therapeutic limits. It is possible that the failure to influence calcification in our series was due to the small dosage employed. Whether larger doses of the irradiated ergosterol will augment calcification of lesions in human tuberculosis is a point for further investigation.

In addition to calcification, the induced lowering of the M/L index by a serological neutralization of the tuberculolipoid, suggested by Doan and Sabin (30), may lengthen the period of survival after tuberculous infection. Another possibility offers itself in the increase of clasmatocytes, which fragment the bacteria readily and rapidly as they do all debris with which they have to deal.

The avoidance of X-rays, with their specific destruction of lymphocytes and consequent increase of the M/L index, has long been indicated (31).

Conservative surgery of tuberculomata of the brain should at the present time be limited to an exploratory operation for the gross identification of the tumor and a decompression when so indicated. Operative removal has resulted fatally with the exception of a few cases. Van Wagenen (17) has mentioned two such cases of Dr. Charles Frazier, one of Dr. Charles Elsberg and another of Dr. Howard Naffziger. To these may be added the cases of Nobecourt, Paraf and Veil (32), which occurred in a child of ten years of age and who was still living four years after operation. E. Sachs (33) reported four cases, one of which was extirpated and three of which were emptied by aspiration, in which there was

postoperative recovery, the length of which he did not state. There is then a total of 9 cases in which operation has been successful for varying lengths of time.

SUMMARY

1. Four cases of solitary tuberculoma of the brain are reported, three in the cerebellum and one in the pons.

2. Since 1790, at least 815 cases of tuberculoma of the brain have been reported.

3. Tuberculomata average 2.5 per cent of all brain tumors.

4. Tuberculomata of the brain, from an analysis of reported cases by decades, shows a decrease from 1870 to 1920, with a new maximum in the decade from 1920 to 1930.

5. In an analysis of 646 cases, tuberculoma of the brain was found to appear in 49.5 per cent of the cases before the age of 10 years and 9 per cent in each of the next three decades.

6. The occurrence of tuberculoma of the brain in males is twice that in females.

7. Solitary tuberculomata are twice as common as the multiple types.

8. The frequency of occurrence of solitary tuberculomata in the total cerebrum is almost equal to that in the cerebellum.

9. The cerebellum is four times as frequent a site for occurrence of tuberculoma as any individual division of the cerebrum.

10. Of all the multiple tuberculomata those with only two sites are more frequent.

11. Calcified tuberculoma of the brain is exceedingly rare, being found in 0.01 per cent of all recorded cases.

12. A discussion is given of the origin of tuberculomata, their relation to the tubercle bacillus and meningitis, and specific treatment.

REFERENCES

(1) ANDERSON: Tuberculoma of the central nervous system, Arch. Neur. & Psych., 1928, xx, 354.
(2) FORD: London Med. Journ., 1790, p. 56.
(3) OGLE: British and Foreign Med.-Chirurg. Rev., 1864, lxviii, 457.
(4) LADAME: Symptomatologie und Diagnostik der Hirngeschwulste, Wurzburg, 1865.
(5) BERNHARDT: Beitrage zur Symptomatologie der Hirngeschwulste, Berlin, 1881.
(6) STEFFEN: Gerhardt's Handbuch der Kinderkrankheiten, v, 1881.
(7) WHITE: Guy's Hospital Reports, 1885–1886, xxviii, 117.
(8) STARR: Tumors of the brain in childhood, Medical News, 1889, liv, 29.
(9) STARR: Brain surgery, William Wood & Co., New York, 1893, p. 202.
(10) BRAMWELL: Intracranial tumors, xiv, 270 pp., Y. J. Pentland, Edinburgh, 1888.

(11) SEYDEL: Verhandlg. der deutschen Gesellsch. fur Chir., 1892.
(12) RAVIART: Les tubercles des peduncles cerebraux, Thesis, Lille, Paris, 1900, 150, 119 pp.
(13) GOUBLOT: Les tubercles du cervelet, These, Étude clinique et anatomo-pathologique, Paris, pp. 99, 1904.
(14) ZAPPERT: Der Hirntuberkel im Kindersalter., Arb. a. d. Neurol. Inst. a. d. Wien. Univers., 1909, xvi, 78.
(15) VALOBRA: I tumori des mesencefalo, studio clinico et anatomico, pp. 209, Torino, S. Lattes & Co., 1910.
(16) FERRIS: Tuberculoma of brain, Jour. Am. Med. Assoc., 1929, xcii, 1670.
(17) VAN WAGENEN: Tuberculoma of brain, its incidence among intracranial tumors and its surgical aspects, Arch. Neur. & Psych., 1927, xvii, 57.
(18) STEWART: Healed tuberculoma of the cerebellum, J. Path. & Bact., 1927, xxx, 577.
(19) TOOTH: Some observations on the growth and survival period of intracranial tumors, Brain, 1912, xxxv, 61.
(20) BECK: Beitr. z. klin. Chir., 1894, xii, 1.
(21) BOLTZ: Ein Beitrag zur Statistik und Anatomie der Tuberkulose im Kindersalter, Inaug. Dis., Kiel, 1890, p. 21.
(22) MARBURG AND RANZI: Arch. f. klin. Chir., 1921, cxvi, 96.
(23) SCHIDLOWSKY: Tuberculoma of the central nervous system, Ibid., 1929, clv, 703.
(24) CLARKE: A study of the anatomic location and histopathology of ninety-nine brain tumors, Rev. Neurol. & Psychiat., 1916, xiv, 485.
(25) DOWMAN AND SMITH: Intracranial tumors, a review of one hundred verified cases, Arch. Neur. & Psych., 1928, xx, 1312.
(26) SCHROTH: Tuberculoma, J. Med. (Cinn.), 1928, ix, 485.
(27) SABIN AND DOAN: The biological reactions in rabbits to the protein and phosphatide fractions from the chemical analysis of human tubercle bacilli, Jour. Exp. Med., 1927, xlvi, 645.
(28) RICH AND MCCORDOCK: An enquiry concerning the rôle of allergy, immunity and other factors of importance in the pathogenesis of human tuberculosis, Bull. Johns Hopkins Hosp., 1929, xliv, 273.
(29) KAMINSKY AND DAVIDSON: The effect of viosterol (irradiated ergosterol) on calcification in pulmonary tuberculosis, Amer. Rev. Tuberc., 1931, xxiv, 483.
(30) DOAN AND SABIN: The relation of the tubercle and monocyte-lymphocyte ratio to resistance and susceptibility in tuberculosis, Jour. Exp. Med., 1930, lii, 113.
(31) MURPHY AND ELLIS: Experiments on the rôle of lymphoid tissue in resistance to experimental tuberculosis in mice, Jour. Exp. Med., 1914, xx, 397.
(32) NOBECOURT, PARAF AND VEIL: Bull. Soc. de Pediat. de Paris, Oct.–Dec. 1926, xxiv, 326.
(33) SACHS: Diagnosis and treatment of brain tumors, C. V. Mosby Co., St. Louis, 1931, p. 182.

SO CALLED PLEUROPULMONARY ENDOTHELIOMA

Report of a Case[1]

ANDREW L. BANYAI AND JOHN GRILL

Primary endothelioma of the lungs is very rare. Most authors believe that it originates in the pleura and secondarily infiltrates the lung diffusely. Robinson (1) contends that the so called endotheliomata of the pleura are really secondary metastases from unrecognized or latent primary carcinomata of the lung. Lord (2) states that the character and histological appearance of the pleural endotheliomata do not, in general, differ from carcinoma in other regions, and he thinks that for this reason, and because their origin in the surface epithelium or lymph-vessel endothelium is too uncertain, the term carcinoma instead of endothelioma is more appropriate for these tumors. He also mentions that there were only three cases studied by himself among 4,704 necropsies at the Massachusetts General Hospital and that there were only 40 to 50 authentic cases reported in the literature up to 1925.

Because of the rarity of this affection the report of a case seems to be justified. No correct diagnosis was established until two months before the patient's death, after an illness of almost two years' duration and a five-month sanatorium stay.

Case Report

E.B.: 26 years old; white; married woman. Family history irrelevant. *Past history:* Measles and chicken-pox during childhood; tonsillectomy at 21 years with uneventful recovery. *Present illness:* In August, 1929, developed a cold, from which she never recovered; had slight cough without expectoration since that time. Shortly afterward contracted pleurisy on right side at base anteriorly; aspirated and sterile pus found; second aspiration with same result two weeks before admission. Transfusion of 500 cc. of blood four months before admission. Lost 18 lbs. in three months prior to admission. *Complaints on admission* (November 24, 1930): Slight cough and mucoid expectoration; heaviness in right side of chest; marked dyspnoea; slight fever and

[1] From Muirdale Sanatorium, Wauwatosa, Wisconsin, and the Milwaukee County General Hospital, Milwaukee, Wisconsin.

night-sweats; loss of weight and strength; ill in bed for one year. *Diagnosis* (of referring physician): Far-advanced pulmonary tuberculosis with empyema.

Physical Examination on Admission: Fairly well nourished, anaemic, weak and dyspnoeic. Temperature 37.3°C.; pulse 128; respiration 30. Thyroid: simple colloid goitre. Fingers clubbed. Other organs except lungs apparently normal. *Lungs:* Right side of chest distended, particularly the lower portion. Interspaces effaced. Respiratory motion practically absent. Tactile fremitus absent throughout right side. Percussion note on same side impaired to 4th rib and 5th dorsal spine; flat below this level. *Left side:* Normal. *Auscultation: Right side:* Distant breath-sounds to 4th rib and 5th dorsal spine; breath-

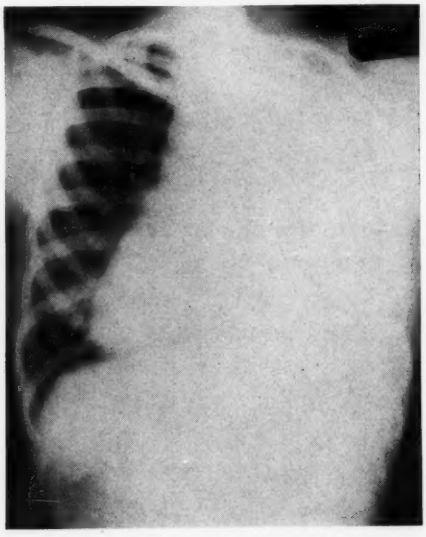


FIG. 1. ROENTGENOGRAM OF LUNGS ON ADMISSION

sounds absent below this level; whispered voice conduction lacking throughout. *Left side:* Normal. *Tentative diagnosis based on physical findings:* Tuberculous empyema, right side; simple goitre. *Report of roentgenologist:* Probably fluid on right side. *Laboratory data on admission:* Sputum negative for tubercle bacilli on five successive examinations. Tuberculin test negative to 1:1000 dilution on two occasions; positive to 1:100 dilution. Wassermann and Kahn reactions of blood negative. *Blood count:* Hgb. 46 per cent; color index 0.6; W.B.C. 19,000; R.B.C. 3,810,000: polymorphonuclears 73; lymphocytes 14.5; monocytes 12.5 per cent. Red-cell sedimentation curve 59 per cent of normal level. Vital capacity 32 per cent of normal. Blood culture negative. Urine normal.

Clinical Observations: 2 cc. of bloody fluid withdrawn from right side of chest shortly after admission: negative for tubercle bacilli. No fluid obtained on several repeated attempts later on. Temperature varying between normal and 38.3°C., pulse between 90 and 120, respirations between 22 and 32. Repeated sputum examinations by homogenization were negative for tubercle bacilli. Routine sanatorium care. Quartz-lamp irradiation for two months. Patient's condition was gradually getting worse. The blood count showed an increase in the white cells up to 34,000, with 82.5 per cent polymorphonuclears. Patient's complaints of malaise, fever, dyspnoea and thoracic pain became more marked in four months. Slight cough with scanty expectoration persisted. It was thought at this time that the patient was suffering from an encapsulated empyema and underlying parenchymal tuberculosis, or from a nontuberculous pulmonary abscess. Thoracoplasty, with removal of the right 7th to 11th ribs was done on March 19, 1931. Surgical findings by Dr. John L. Yates: A mass the size of a fist, thought to be an induration of a cavity within the lung, was found at the level of the centre of the eighth rib posteriorly; this was aspirated. The aspirated fluid was negative for tubercle bacilli. Guinea-pig inoculation with the same fluid was negative for tuberculosis. Three transfusions followed at short intervals, but with no appreciable change in the red-blood-cell count. The leucocytes decreased to 14,000, the polymorphonuclears being practically the same as before. The temperature noticeably declined following operation, and emesis was noticed every four to five days afterward. At the next periodic examination several dilated and enlarged skin veins originating from the lower part of the chest and ending in the right inguinal region with a flow downward were seen. At the same time an enlarged lymph node, the size of a hazel-nut, was noticed in the right axilla. A tentative diagnosis of pulmonary malignant tumor was made at this time. A second thoracoplasty with removal of three more ribs was performed as a preliminary measure to cautery pneumonectomy on April 30, 1931. A pulmonary abscess, the size of an orange, was incised and drained by three drainage-tubes. Tissue from a pulmonary nodule was obtained for histological examination. Pus removed from the cavity was negative for tubercle bacilli; gram-stained slides were also negative. Two weeks later direct deep X-ray irradiation was applied over the tumor found at first operation, the chest-wall being opened and retracted. The surgeon stated that the tumor felt smaller and all lung tissue encountered felt atelectatic; the cavity found at the second operation collapsed materially and its walls became sclerotic. With the exception of a one-day postoperative rise, the temperature stayed practically normal with a pulse-rate of 100 to 120 for two weeks, when the patient again became febrile. She left the institution on June 23, 1931. Her complaints were severe dyspnoea, thoracic pain, cough, gastric distress and malaise. She died three weeks later. No postmortem examination was done.

Microscopic Findings: The small pieces of tissue obtained during operation were fixed in formalin. Paraffin sections were stained with haematoxylin-eosin and by Van Gieson's method. The histological examination showed the tumor to be made up of cells, the majority of which were of epithelial character. These were arranged in longitudinal rows and less frequently in an alveolar manner. The cell-form presented itself in a marked variety; some of the cells appeared flat and somewhat elongated, giving the impression of being compressed; others were round and polyhedral. The cytoplasm was not very abundant; it stained light red with eosin and its boundary was not always distinct. The nuclei stained rather light and were vesicular in character. There

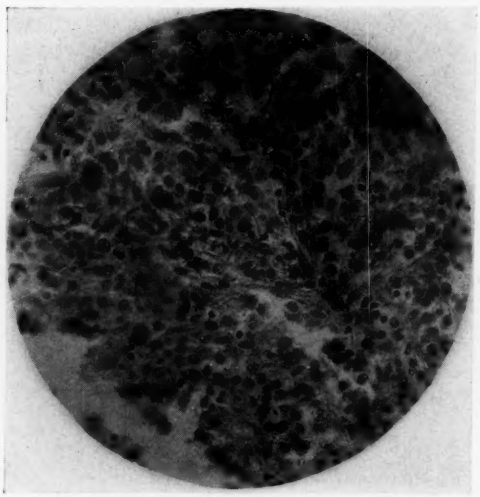


FIG. 2. LOW-POWER MICROPHOTOGRAPH OF PLEUROPULMONARY MESOTHELIOMA
See details in histological report.

was, however, a distinct nuclear membrane evident. The nucleoli were very distinct. Some of the cells contained one, others two or more nucleoli. Throughout the sections mitotic figures could be seen. Here and there giant cells were scattered among the tumor cells. The giant cells were found more frequently in areas in which the stroma was more abundant. In sections stained by Van Gieson's method very delicate intercellular fibrils could be demonstrated that surrounded the tumor cells and were in close proximity to the cytoplasm of the cells. The stroma was not very abundant and contained few leucocytes and lymphocytes. The capillaries were very thin.

The histological structure of the tumor suggested partly an epithelial and partly a connective-tissue neoplasm. Since there was no evidence during the entire course of the disease of any neoplasm in any other part of the body, it

may be reasonably assumed that this was a case of a primary tumor of the pleura which gradually penetrated the right lung.

Klemperer and Rabin (3), who recently reviewed the question of primary tumors of the pleura, classify these neoplasms into two groups: (1) the localized tumors of the pleura which are of mesenchymal origin, and (2) the diffuse tumors which arise from the surface lining cells of the pleura and are of mesothelial origin. These cells are not of endothelial character; therefore the old term *endothelioma* is not correct for designating such tumors.

According to the investigations of Broman (4) the cells of the serous membranes, such as the pleura, pericardium and peritoneum, arise from segregated

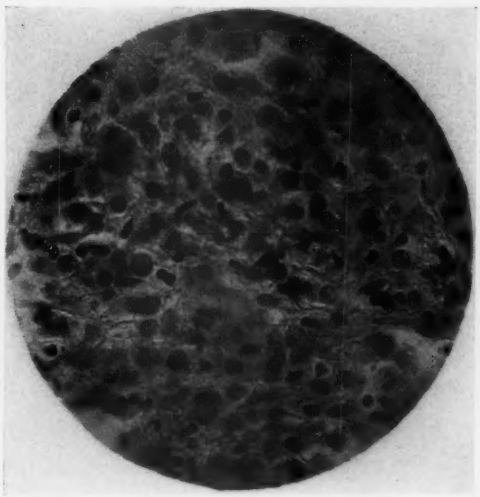


FIG. 3. HIGH-POWER MICROPHOTOGRAPH OF PLEUROPULMONARY MESOTHELIOMA
See details in histological report.

cells of the mesoderm lining the celomic cavity. Histologically these cells are epithelial in appearance. There are, however, differences between these and the ordinary epithelial cells; therefore the name of *mesothelial cells* and *mesothelium* was suggested.

It was shown by Maximow's investigations on tissue-cultures (5) that the lining cells of the pleura may develop into epithelial and connective-tissue cells. The findings of Maximow clearly explain the fact that such tumors of the pleura are described in the literature under various names and are called by some carcinomatous, by others sarcomatous new growths, according to the predominating morphological characteristics of the tumor cells.

The microscopic picture, as seen in the sections and presented in the accompanying microphotographs, is interpreted as that of mesothelioma.

COMMENT

The history of acute onset was thought to be an indication of an inflammatory process. Many instances of pulmonary malignant tumor, however, are described with an acute onset and accompanied by pain in the chest or induced by a febrile attack. Patients with early symptomless lung tumors may become conscious of their pulmonary disease following influenza or other severe disease of the lungs, because such a disease may increase the bronchial stenosis already present to a symptom-producing degree. The presence of empyema with sterile pus was taken as evidence of the tuberculous nature of the disease. Idiopathic empyema in patients past middle age may be the first clinical manifestation of pleuropulmonary malignant tumor.

Stivelman (6) aptly says that there can be no doubt that fewer pulmonary neoplasms will be missed if spontaneous empyemata, interlobar and pulmonary abscesses not dependent on a metapneumonic process, are viewed with suspicion and subjected to careful scrutiny when they occur in patients past middle life. The same observance should be exerted in younger persons with similar conditions, when there is a marked discrepancy between symptomatology on the one hand and physical and X-ray findings on the other. The mistake was committed in connection with the aspiration that the pus withdrawn was not examined for the presence of fat-containing epithelial cells or tumor cells found eventually in malignant pleural effusions. Heaviness in the right side and dyspnoea were supposed to be caused by a large tuberculous effusion. Still, after several unsuccessful aspirations (only once was 2 cc. obtained at this institution), with the history that dyspnoea and thoracic pressure were not relieved by previous aspirations, we should have thought of malignant tumor in the presence of other suggestive data.

Our patient had moderate, irregular, remittent fever, not unlike that seen in pulmonary tuberculosis, and probably caused by the absorption of toxic substances from the tumor area, atelectatic portions or regions invaded by secondary infection.

Fremont-Smith (7) found clubbing of the fingers in 27 per cent of his pulmonary cancer cases. Progressively expanding neoplastic growths may cause bulging of the hemithorax and increase in the costal interspaces. Such an enlargement is not unlike that seen in large tuberculous pleural effusions. The percussion note over large thoracic tumors is flat and occasionally may give a peculiar sensation of solid resistance not

found over large effusions. This sign was detected during the last two months of the disease in this patient.

Patients with pulmonary malignant tumor rarely react to tuberculin or only to large doses. Variations in the blood-picture do not represent additional help in diagnosis. Anaemia may or may not be present. There is no definite relationship between the extent of involvement and the degree of anaemia. Leucocytosis with a relative polymorphonucleosis should be interpreted as a sign of toxin absorption with or without secondary infection. The red-cell sedimentation speed is increased in both tuberculosis and pulmonary neoplasm. Evidence of gradual compression of one of the larger thoracic veins was manifested by the appearance of dilated, enlarged skin veins over the right side of abdomen that carried blood from the chest indirectly to the inferior vena cava. Simultaneously the patient also developed a stridor because of gradual compression of the large bronchi. The patient did not develop detectable metastases during her stay except in the right axillary lymph nodes.

Roentgenography is one of the most valuable methods for diagnosing malignant disease of the lung. The induction of artificial pneumothorax may aid the roentgenologist in his diagnostic work. Bronchoscopy and thoracoscopy are of great value in experienced hands in suspected cases when there is a reasonable chance to get additional diagnostic information. It is the opinion of Sauerbruch (8) that because the diagnosis of pulmonary malignant tumor is difficult in many instances, it is necessary to open the chest to establish the diagnosis, just as the abdomen is subjected to exploration. He states that such exploratory operations are attended by minimal danger and suggests that the patients must be persuaded not to avoid operation, for without it one may often miss the proper time when surgical intervention might be successful.

REFERENCES

(1) Robinson: Quoted by Miller, J. A., and Jones, O. R.: Primary carcinoma of the lung, Amer. Rev. Tuberc., 1930, xxi, 1.

(2) Lord, F. T.: Diseases of the bronchi, lungs, and pleura, Lea & Febiger, Philadelphia & New York, 1925.

(3) Klemperer, P., and Rabin, C. B.: Primary neoplasms of the pleura, Arch. Path., 1931, xi, 385.

(4) Broman, J.: Grundriss der Entwickelungsgeschichte d. Menschen.

(5) Maximow, A.: Arch. experim. Zellforschung, 1928, iv, 1.

(6) Stivelman, B. P.: The roentgen ray in the diagnosis of primary pulmonary neoplasm, Jour. Am. Med. Ass., 1928, xci, 1690.

(7) Fremont-Smith, M., Lerman, J., and Rosahn, P. D.: Primary carcinoma of the lungs, New Eng. J. Med., 1930, cciii, 473.

(8) Sauerbruch, F.: Budapest letter, Jour. Am. Med. Ass., 1930, cxiv, 423.

THE EFFECTS OF THORACOPLASTY ON THE HEART[1]

OLGA S. HANSEN[2] AND HENRY W. MALY

In an attempt to determine the cardiac efficiency of tuberculous patients about to undergo thoracoplasty and the possibility of cardiac damage following this operation, 57 cases have been selected for special study out of the 161 who have had such collapse at Glen Lake Sanatorium. Many patients have been observed over a period of three and one-half years with frequent electrocardiograms and examinations at the various stages of collapse. However, in the 57 cases analyzed in this report, only the electrocardiogram taken before the first stage of the operation and the one taken after the completion of collapse have been compared along with the X-rays of approximately the same dates.

A number of these patients have been reported in a previous paper after pneumothorax or phrenic exairesis, and have by now reached the thoracoplasty stage of collapse (1). Although the fibrosis, retraction and deformity following the surgical collapse has been considered the important factor in determining heart position, other conditions, such as pleural effusion or empyema, bed-rest, and loss of muscular tone must be taken into account as possible causes for variability of electrocardiographic waves.

It was to be expected that intrathoracic changes associated with thoracoplasty would affect principally the amplitude of the Q R S waves, since previous studies had revealed a large incidence of variations in the Q R S voltage and practically none in the other waves. The 57 cases were therefore grouped according to the degree and type of Q R S change. In many cases each electrocardiogram considered separately would have been pronounced normal, but the changes in the R and S amplitude were such as to suggest a shift of the electrical axis in the left or right direction. These findings were rarely marked enough to permit a diagnosis of abnormal right or left preponderance. Group 1 comprises those showing no significant change in the Q R S amplitude. Groups 2, 3 and 4 reveal respectively slight, moderate, and marked changes. Groups 5 and 6

[1] From the Glen Lake Sanatorium, Oak Terrace, Minnesota.
[2] The Medical Division, Nicollet Clinic, Minneapolis, Minnesota.

represent the cases showing electrocardiographic evidence of a shift toward the left and the right respectively. Changes in P and T waves were seen so infrequently that their consideration has been disregarded.

TABLE 1

Group 1 (21 = 37 per cent): no electrocardiographic change

NUMBER	PREOPERATIVE ECG.	PREOPERATIVE X-RAY	POSTOPERATIVE X-RAY	X-RAY CHANGE
		Right thoracoplasty = 12		
1	Rt. ax. dev.	Normal	Left 1	Left 1
2	Rt. ax. dev.	Normal	Left 1	Left 1
3	Rt. ax. dev.	Right 1	Normal	Left 1
4	Lt. ax. dev.	Normal	Normal	0
5	Normal	Normal	Normal	0
6	Normal	Normal	Normal	0
7	Normal	Normal	Normal	0
8	Normal	Normal	Left 1	Left 1
9	Normal	Right 1	Normal	Left 1
10	Normal	Normal	Left 1	Left 1
11	Normal	Right 3	Normal	Left 3
12	Normal	Right 3	Normal	Left 3
		Left thoracoplasty = 9		
1	Rt. ax. dev.	Normal	Normal	0
2	Rt. ax. dev.	Left 1	Right 2	Right 3
3	Lt. ax. dev.	Left 1	Right 2	Right 3
4	Normal	Normal	Right 1	Right 1
5	Normal	Normal	Right 1	Right 1
6	Normal	Left 1	Normal	Right 1
7	Normal	Left 2	Normal	Right 2
8	Normal	Left 3	Left 1	Right 2
9	Normal	Left 1	Right 4	Right 4+

Note: The degree of change of heart position from the normal before and after collapse is indicated by the numerals 1 to 4 (slight, moderate, marked and extreme).

Group 1 comprises 21 patients (37 per cent) who showed no significant change in the Q R S amplitude following thoracoplasty, 12 right-sided and 9 left-sided (table 1). Of the right-sided, three gave electrocardiographic evidence of a right axis deviation which remained unchanged in spite of the fact that the heart was displaced slightly to the left by the collapse. The one with a left axis deviation, unchanged after operation,

showed no change in the heart position. In the eight with constantly normal electrocardiograms, X-ray films indicated no change in three, slight change toward the left in three, and marked change toward the left in two. Of the left-sided group, two showed a right axis deviation in the electrocardiogram, with no X-ray evidence of postoperative change in position in one and a marked change in the other toward the right. The heart position was displaced markedly toward the right in the one case with a slight left axis deviation. The cases with normal preoperative electrocardiograms showed a slight change in three, a moderate change in two, and an extreme displacement in one, toward the right (unaffected) side.

Group 2 consists of 22 cases (38+ per cent), ten right-sided and twelve left, in which the electrocardiogram showed a slight change in the Q R S amplitude after thoracoplasty (table 2). Of the 10 right-sided cases two showed electrocardiographic evidence of a shift toward right axis deviation, and three toward left postoperatively. In the other five the increase or decrease in the Q R S amplitude did not suggest any deviation of the electrical axis. X-ray studies indicated no change in the heart position in 4 cases and a slight shift to the left (unaffected) side in two, moderate in one and marked in one. One moderate change toward the right and one marked was noted. In only 2 cases was there an agreement between electrocardiogram and X-ray in that the left axis deviation appearing after thoracoplasty was associated with definite displacement of the apex of the heart toward the left. In the 12 left-sided cases, electrocardiograms suggested a shift of the electrical axis toward the right in seven and toward the left in three after operation. X-ray studies showed a displacement toward the right in 8 cases, five slight, one moderate and two marked; toward the left in three, two slight and one marked; and in one case the heart position was unchanged. In 7 cases electrocardiograms and X-rays agreed, in three disagreed, and in two the electrocardiographic changes were not characteristic.

Group 3 consists of 5 cases (8+ per cent), two right-sided and three left-sided, showing moderate changes in the Q R S voltage, with only one showing a definite development of a left axis deviation concomitant with a slight retraction of the heart toward the affected side (left). (Table 3.) Another case showed an increase in a previously existing left axis deviation in the face of a marked displacement of the heart toward the right (unaffected) side. A shift of the axis toward the right was

associated with a slight displacement toward the left (unaffected) side in one case.

TABLE 2

Group 2 (22 = 38 per cent): slight electrocardiographic change

NUMBER	ELECTROCARDIOGRAM		X-RAY			X-RAY AND ECG. AGREEMENT
	Preoperative	Postoperative	Preoperative	Postoperative	Change	
		Right thoracoplasty = 10				
1	Tendency Rt. ax. dev.	Right	Normal	Normal	0	−
2	Normal	Right	Left 1	Right 1	Right 2	−
3	Normal	Left	Normal	Left 3	Left 3	+
4	Normal	Left	Normal	Left 2	Left 2	+
5	Normal	Left	Normal	Right 3	Right 3	−
6	Normal	Decr. QRS 1	Normal	Left 1	Left 1	±
7	Normal	Decr. QRS 1–2–3	Normal	Normal	0	±
8	Normal	Incr. QRS 3	Normal	Left 1	Left 1	±
9	Normal	Decr. QRS 2	Left 1	Left 1	0	±
10	Normal	Incr. QRS 3	Left 1	Left 1	0	±
		Left thoracoplasty = 12				
1	Rt. ax. dev.	Incr. rt.	Left 1	Right 1	Right 1	+
2	Normal	Right	Left 2	Right 1	Right 3	+
3	Normal	Right	Normal	Left 1	Left 1	−
4	Normal	Right	Normal	Right 1	Right 1	+
5	Normal	Right	Right 1	Right 3	Right 2	+
6	Normal	Right	Left 2	Left 1	Right 1	+
7	Normal	Right	Normal	Right 1	Right 1	+
8	Normal	Left	Right 3	Normal	Left 3	+
9	Normal	Left	Normal	Normal	0	−
10	Normal	Left	Normal	Right 1	Right 1	−
11	Normal	Decr. volt.	Right 1	Normal	Left 1	±
12	Normal	Incr. R 1 Decr. R 2–3	Left 3	Normal	Right 3	±

Group 4 consists of 9 cases (16 per cent), five left-sided and four right, in which marked changes appeared in the amplitude of the Q R S waves following collapse. (Table 4.) In only two did the heart position change toward the left or the right in agreement with the electrocardio-

gram. In three the electrocardiogram suggested a shift opposite to what actually occurred in the heart position. Four of the electrocardiograms

TABLE 3

Group 3 (5 = 8 per cent): moderate electrocardiographic change

NUMBER	ELECTROCARDIOGRAM		X-RAY			X-RAY AND ECG. AGREEMENT
	Preoperative	Postoperative	Preoperative	Postoperative	Change	
Right thoracoplasty = 3						
1	Normal	Rt. ax. dev.	Right 1	Normal	Left 1	−
2	Normal	Decr. R1 S3	Normal	Normal	0	±
3	Normal	Incr. QRS 1–2–3	Normal	Left 1	Left 1	±
Left thoracoplasty = 2						
1	Lt. ax. dev.	Incr. lt.	Left 1	Right 2	Right 3	−
2	Normal	Lt. ax. dev.	Right 1	Normal	Left 1	+

TABLE 4

Group 4 (9 = 16 per cent): marked electrocardiographic change

NUMBER	ELECTROCARDIOGRAM		X-RAY			X-RAY AND ECG. AGREEMENT
	Preoperative	Postoperative	Preoperative	Postoperative	Change	
Right thoracoplasty = 4						
1	Rt. ax. dev.	Normal	Normal	Right 1	Right 1	−
2	Normal	Left	Normal	Left 1	Left 1	+
3	Normal	Incr. QRS 1–2–3	Left 1	Left 2	Left 1	±
4	Normal	Incr. QRS 1–3	Right 1	Left 1	Left 2	±
Left thoracoplasty = 5						
1	Normal	Incr. volt.	Left 3	Right 1	Right 4	±
2	Normal	Shift left	Normal	Normal	0	−
3	Normal	Shift right	Right 1	Normal	Left 1	−
4	Normal	Shift left	Normal	Right 1	Right 1	+
5	Normal	Incr. volt.	Normal	Right 2	Right 2	±

showed an increase in the Q R S voltage not characteristic of an axis deviation.

Group 5 (table 5), twelve cases collected from groups 2, 3, and 4 with electrocardiographic evidence of a shift of the axis toward the left (5

TABLE 5

Group 5 (12 cases): shift of axis toward left

NUMBER	ELECTROCARDIOGRAM		X-RAY			X-RAY AND ECG. AGREEMENT
	Preoperative	Postoperative	Preoperative	Postoperative	Change	
Right thoracoplasty = 5						
1	Normal	Left II	Normal	Left 2	Left 2	+
2	Normal	Left II	Normal	Left 3	Left 3	+
3	Normal	Left IV	Normal	Left 1	Left 1	+
4	Normal	Left II	Normal	Right 3	Right 3	−
5	Rt. ax. dev.	Normal	Normal	Right 1	Right 1	−
Left thoracoplasty = 7						
1	Normal	Left II	Right 3	Normal	Left 3	+
2	Normal	Left III	Right 1	Normal	Left 1	+
3	Normal	Left IV	Normal	Right 1	Right 1	+
4	Normal	Left II	Normal	Normal	0	−
5	Normal	Left II	Normal	Right 1	Right 1	−
6	Lt. ax. dev.	Left III	Left 1	Right 2	Right 3	−
7	Normal	Left I	Normal	Normal	0	−

TABLE 6

Group 6 (12 cases): shift of axis toward the right

NUMBER	ELECTROCARDIOGRAM		X-RAY			X-RAY AND ECG. AGREEMENT
	Preoperative	Postoperative	Preoperative	Postoperative	Change	
Right thoracoplasty = 4						
1	Normal	Right III	Right 1	Normal	Left 1	−
2	Normal	Right II	Left 1	Left 1	0	−
3	Normal	Right II	Left 1	Left 2	Left 1	−
4	Rt. ax. dev.	Right II (incr.)	Normal	Normal	0	−
Left thoracoplasty = 8						
1	Rt. ax. dev.	Right II (incr.)	Left 1	Right 1	Right 1	+
2	Normal	Right II	Normal	Right 1	Right 1	+
3	Normal	Right II	Right 1	Right 2	Right 2	+
4	Normal	Right II	Left 2	Left 1	Right 1	+
5	Normal	Right II	Normal	Right 1	Right 1	+
6	Normal	Right II	Left 2	Right 1	Right 3	+
7	Normal	Right II	Normal	Left 1	Left 1	−
8	Normal	Right IV	Right 1	Normal	Left 1	−

right-sided collapse and 7 left), showed the heart displaced in the same direction six times, in the opposite direction four times, and unchanged in position twice. One right axis deviation prior to operation became normal later, indicating a shift of the axis toward the left, although the heart had been displaced slightly toward the right.

In group 6 (shift of axis toward the right) (table 6), 12 cases showed electrocardiographic signs of a shift of the axis deviation toward the right, 10 slight, one moderate and one marked. In 6 cases the heart had been displaced toward the right, in four toward the left and in two it remained unchanged. In the 2 cases with the most marked right axis deviation after collapse, the heart had been displaced slightly toward the left.

X-RAY CHANGES FOLLOWING THORACOPLASTY

In many cases the heart was displaced from its normal position by the pulmonary pathological process or by collapse procedure prior to the thoracoplasty. Taking this as a standard for comparison with the postoperative condition, it was found to be unchanged in twelve (21 per cent), while twenty-seven (47 per cent) showed a slight change, six (10 per cent) a moderate, ten (17 per cent) a marked and two (3+ per cent) an extreme degree of displacement. Thoracoplasty displaced the heart from its preoperative position not at all or only slightly in 39 cases (68 per cent). Including the large group of twenty-seven with slight change only, some degree of displacement took place in forty-nine (87 per cent).

Displacement of the heart in right thoracoplasty was about evenly divided between the right and left directions; toward the right (affected side) eleven, and toward the left nine times, while in left thoracoplasty there was a marked preponderance of right-sided displacement (toward the unaffected side) (right 21 and left 4). Apparently right-sided operation may either pull or push the heart, while left-sided collapse pushes about five times as often as it pulls.

AUTOPSY FINDINGS

Twenty-four hearts of patients with collapse by thoracoplasty who came to autopsy have been studied microscopically by Dr. C. C. Van Winkle, Pathologist, and have shown no more evidence of degenerative changes than have 52 hearts in other patients dying of tuberculosis. Death occurred from one day to five years following the last operation,

the average time being six months. Pathological studies on a series of hearts of tuberculous patients to be reported later by Dr. Van Winkle indicate that there are no heart findings characteristic for tuberculosis. The weight averaged 258 gm. in the women and 367 gm. in the men in the thoracoplasty group. Fifty-two recent autopsies on 25 women and 27 men dying of tuberculosis without previous thoracoplasty showed average heart weights of 236 and 298 gm. respectively.

CONTROL PATIENTS WITHOUT COLLAPSE

Of 30 patients with uncomplicated pulmonary tuberculosis without collapse therapy, observed by means of the electrocardiogram for a period of four months to a year, fourteen (46 per cent) showed no evidence of electrocardiographic change, eight (26 per cent) slight change, four (13 per cent) moderate and four (13 per cent) marked change. Comparative percentages in the thoracoplasty series are 37, 38, 8 and 16 respectively. While slight or no change occurred in both groups with about equal frequency, moderate more frequently in the control and marked more frequently in the collapse cases, the difference is too small to be conclusive.

SUMMARY

1. In an attempt to determine the effects of thoracoplasty on the heart as evidenced by the electrocardiogram, 57 cases have been studied by means of electrocardiograms and X-ray films before and after the collapse. Thirty cases of uncomplicated pulmonary tuberculosis have been taken for controls.

2. Twenty-one (37 per cent) of the operated and fourteen (46 per cent) of the unoperated cases showed constant electrocardiograms. Twenty-two (38 per cent) and eight (26 per cent) respectively showed slight changes; five (8 per cent) and 4 (13 per cent) moderate; and nine (15 per cent) and four (13 per cent) marked variation in Q R S amplitude.

3. The heart position, as shown by X-ray films, was unchanged after thoracoplasty in 12 cases (21 per cent), slightly changed in twenty-seven (47 per cent), moderately in six (10 per cent), markedly in ten (17 per cent) and extremely in two (3 per cent).

4. In the 36 cases showing electrocardiographic change twelve (33 per cent) gave X-ray evidence of a change in heart position in the same direction, though not necessarily of the same degree. In 11 cases the electrocardiograms and X-rays disagreed and in thirteen they were indeterminate.

COMMENTS

It has been shown in this series that the intrathoracic pathological involvement incident to thoracoplasty almost invariably (in 87 per cent) displaces the heart more or less to one side or the other, but more frequently toward the unaffected side. The electrocardiograms also show a high incidence of postoperative change (63 per cent, including the slight ones), but these changes are neither consistent nor predictable, being in agreement with the X-ray findings in only a third of the cases. It would seem impossible to predict the probable electrocardiographic change from a study of the X-rays, or conversely to guess the type of X-ray findings from looking at the electrocardiograms.

It is probable that the electrical axis may be influenced by rotation of the heart on its longitudinal axis by fibrotic tissue affecting at times the base and at times the apex anteriorly or posteriorly, as has been shown experimentally by Meek and Wilson (2) and others.

It is probable that other factors such as bed-rest, toxaemia, and weight-changes may affect the form of the electrocardiogram, since the control patients who had no gross mechanical changes were also variable in their complexes.

There has been no evidence of disturbance in conduction or of myocardial damage in electrocardiograms. Autopsy has shown no abnormality in heart-weight nor more evidence of myocardial degeneration than is found in other patients dying of tuberculosis. Some of the changes in Q R S amplitude probably represent changes in muscle-tone associated with reduction in toxaemia and increase in exercise and would appear regardless of the mechanics of collapse. The changes found in the electrocardiogram are probably due to extrinsic factors and bear no relationship to the condition of the heart-muscle.

BIBLIOGRAPHY

(1) HANSEN, O. S., AND KING, F. W.: The influence of pulmonary collapse on the electrocardiogram, Amer. Rev. Tuberc., 1930, xxvi, no. 3.

(2) MEEK, W. J., AND WILSON, A.: The effect of changes in position of the heart on the Q R S complex of the electrocardiogram, Arch. Int. Med., 1925, xxxvi, 614.

THE DIETARY TREATMENT OF SKIN TUBERCULOSIS

S. BOMMER[1]

In 1925 Sauerbruch and Herrmannsdorfer for the first time exhibited a considerable number of patients with the most diversified types of tuberculosis (lung, bone, lymph nodes, skin), who had been either cured, or at least greatly improved, under a special diet. This diet, founded on these investigators' own researches and on Gerson's previous labors, was introduced by me, early in 1928, into the Giessen Lupus Sanatorium for the treatment of the large number of tuberculous skin cases in that institution.

The Herrmannsdorfer-Sauerbruch dietary treatment of tuberculosis possesses the following characteristics:

Common salt is banished entirely in the preparation of foods. Meat is restricted to a total weekly intake of 500–600 gm. Naturally, smoked meat, sausage and boiled ham, as well as smoked and pickled fish are prohibited. The protein requirement is covered, apart from milk, eggs and cheese, mainly by vegetable protein. The diet furnishes a generous amount of fat and is carbohydrate-poor. Contrary to Voit's formula, which provides a daily intake of 118 gm. protein, 56 gm. fat, and 500 gm. carbohydrate, for a medium-weight workman (67 kg.), the tuberculosis diet allows about 90 gm. protein, 162 gm. fat and 222 gm. carbohydrate. For every kilogram of bodyweight about 45–50 calories per day are given. Therefore a patient having an average weight of about 60 kg. will receive 2700–3000 calories daily.

Importance is attached to a generous intake of fresh fruit, salad and vegetables in such a form that their constituents are changed as little as possible by their preparation. Vegetables must be steamed instead of being boiled. A part of the vegetables is given raw. Only fresh vegetables may be used and juices extracted from raw vegetables are added to the soups. As a fat, fresh, sweet dairy butter is preferred. Milk soups, prepared with rice, cream of wheat, tapioca, barley and oatmeal, are given regularly in the morning and at night.

[1] Privatdozent, Giessen, Germany; now Berlin, Charité.

According to Gerson's original directions a mineral mixture was given by mouth three times daily after meals in teaspoonful doses. It consisted of ten different salts including calcium, magnesium and strontium, and was intended to modify the body's mineral economy. Its use has proved superfluous. The use of phosphorized codliver oil has proved useful but not necessary.

Under the influence of this diet, without any other treatment, tuberculous skin foci heal completely. The following observations are made during the course of the nutritional therapy. Already in from 3 to 4 weeks after the treatment is started tuberculous skin ulcers begin to dry out. Thick scabs form on them, which drop off after 3 to 6 more weeks, leaving smooth and little perceptible cicatrices. But the most interesting and characteristic observations are those in the involution of lupus vulgaris. In its typical form lupus vulgaris is characterized by lentil-sized, yellowish-brown infiltrates, which lie scattered more or less densely and in larger or smaller number over the disease focus. The vicinity of these lupus nodules shows more or less oedematous swelling and bluish-red discoloration in different cases. The first distinctly observable phenomenon in such a lupus focus, under the dietary treatment, occurs in from 2 to 3 weeks after its commencement; namely, lessening swelling in the vicinity of the lupus nodules, and disappearing oedema. Simultaneously therewith the color of the vicinity changes, and the bluish-red discoloration disappears and is frequently replaced by a bright, delicate redness of the vicinity of the nodules and of the nodules themselves. In the course of the following 2 to 3 weeks this brighter redness likewise disappears. By then the vicinity of the individual nodules has become quite pale and shows no swelling. The lupus infiltrates persist in this state 2 to 3 weeks longer, whereupon they slowly "melt," and are absorbed by their surroundings. Just as when a drop of water, allowed to fall upon a dry water-color, causes the colors at the drop's periphery to mix gradually with the adjacent colors, so the individual lupus nodule "melts" with ever-increasing indistinctness of its outline, and is finally absorbed by the skin without leaving a trace. Even when there is extensive oedematous infiltration of all cutaneous layers in the domain of a lupus patch, such as we find chiefly in lupus of lips and legs, the first and striking phenomenon is retrogression and disappearance of oedema. The individual lupus nodules are absorbed one by one without leaving a trace. Here and there in the disease-focus one infiltrate after another is extinguished. The manner of involution is

always the same, though its period varies in different patients, like under other methods of treatment. Some cases are obstinate and require longer treatment before distinct involution phenomena manifest themselves. That applies particularly to children with pasty, watery, or cyanotic skin. In patients with a primarily defective vascular system the involution of lupus under the dietary treatment is likewise below the average.

Where there is X-ray injury of the skin, which we unfortunately see very frequently nowadays in lupus patients, these injured skin areas also show changes under the diet. The coarse, doughy, scleroderma-like condition of the skin, which is often present in such cases, begins to involute at times after a few days but always within the first few weeks. With diminishing swelling the skin becomes more motile and is released equably from its foundation, on which it previously rested more or less immovably and could not be folded. The translucent yellow color of these foci disappears. Gradually the teleangiectases decrease in number and extension. The appearance of the previously very prominent skin region thereby more and more conforms to that of the surrounding skin, though not completely.

The diet was also found to influence distinctly the so called hypertrophic cicatrices. These approach the general level of the surrounding skin more and more until they finally attain it wholly or nearly so. Only with decreasing oedema, under the influence of the diet, do we realize the part played by swelling and oedema in hypertrophic cicatrices, lupus and X-ray injury.

Lupus of the mucosa responds to the nutritional treatment at times even better than, but at least as well as that of the skin. Lupus foci in the nasal mucosa, the palate, the pharynx, and also in the larynx, heal under the dietary treatment. In these cases, also, swelling and dark redness lessen; the individual infiltrates then first become more prominent before being absorbed by the vicinity. Ulcers, the same as skin ulcers, show diminished secretion, less covering, formation of bright red granulations, and finally delicate, smooth skinning. Foci of *tuberculosis miliaris ulcerosa*, whether of the mucosa or the neighboring skin, are less favorably influenced, according to my present experience, than lupus foci.

Diminishing oedema and disappearance of venous stasis are the first clinically demonstrable effects of the diet on the cutaneous lupus foci. They precede all other phenomena, such as indistinctness, "melting," and absorption of the nodules. In connection with the observations

which are made in X-ray injury and hypertrophic cicatrices, the assumption can be made that a material factor of the dietary effect consists in an influence on the vascular system of the diseased areas. An influence on the vascular system, improved circulatory conditions and restoration of the disturbed water exchange between vascular system and tissue are obviously the first effects of the tuberculosis diet in the disease focus. That view is supported also by the obstinate behavior of foci in children with pasty or generally cyanotic skin, and also by the more prolonged duration of the dietary treatment where the vascular system is primarily defective.

The vascular wall, particularly the capillary wall, is the site at which the diet and its factors probably first become operative. There the diet's primary action, which restores the function of the capillary-wall cells wholly, partly or approximately, becomes effective. All other curative processes may, in my opinion, be regarded as sequellae of this action on the capillary wall and its cells. On the other hand, the great importance of the capillary-wall cells in the inflammatory region is being increasingly recognized. Thus, G. Herzog believes that the epithelioid and giant cells of the typical tubercle are probably also derived from the cells of the capillary walls. Babes, too, has shown the development of tuberculous giant cells from proliferated capillary endothelium. The observations and views of Borst, Broden, Mueller, Oppenheimer and Lubarsch coincide herewith. In inflammation, under the different functional stimuli, the cellular forms which are more or less characteristic of the particular cause, are derived from the cells of the vascular walls (G. Herzog).

Among the individual factors of the Herrmannsdorfer-Sauerbruch diet which might be effective, the most impressive is the salt poverty of the food. The question thus arises whether salt withdrawal is to be regarded as the most essential and decisive factor of this diet. This is probably to be negatived. In the Giessen Lupus Clinic 10 female patients were fed on the customary staff meals, that is, on a relatively vitamine-poor diet, the only difference being that no common salt was added to the foods. In none of these patients were any curative processes observed which could be compared with those obtained under the Herrmannsdorfer-Sauerbruch Diet. The other question, that is, whether the vitamines contained in the diet constitute the chief curative factor is likewise to be negatived. Blumenthal gave lupus patients a vitamine-rich diet to which common salt was added, and also vigantol. These

patients also showed no successful results; no influence of their diet on the lupus foci was determinable. Salt withdrawal and vitamine-intake (in the opinion of the majority the most important factors of the tuberculosis diet) fail wholly or nearly so when either of them is administered separately.

But we know of no other factor which might be considered sufficiently potent to entitle it to have the chief influence on the tuberculous focus ascribed to it. Consequently there remains no choice, in our present knowledge, but to assume that salt withdrawal and vitamine-intake must take place simultaneously; that, if the curative processes in the foci of skin tuberculosis are to be brought about, a diet must fulfil these two conditions. Only under the influence of salt regulation, and only after the normal physiological ionic environment of the vascular wall cells has been restored, are the vitamines able to unfold their full effects. Salt regulation and vitamine-intake obviously promote and support each other's action.

When we speak of salt regulation in this connection, it should be asked whether this may not be attained otherwise than by salt withdrawal. Bunge used to teach that a daily intake of more than 2 gm. of common salt merely serves the palate. But this object should not be deprecated when the superior palatability of patients' food is involved. This is attainable even without adding any common salt, as shown by Mrs. Herrmannsdorfer, but then demands special culinary skill and a particularly intelligent and reliable kitchen personnel. In connection herewith it is interesting to note that several sport-loving patients informed me individually and spontaneously that their muscular capabilities declined during the dietary treatment. This recalls Overton's observations, according to which the sodium cation is mainly responsible for the restoration of muscular excitability in the surviving frog's muscle. Further, v. Weiss and also Gruenwald investigated the action of experimentally induced chlorine deficiency in rabbits. He observed tremors followed by paralysis. Whether the sodium cation is related to the muscular and the chlorine anion to the central-nervous excitability in this condition remains uncertain.

On the other hand numerous researches have taught us that pure sodium-chloride solution acts toxically on animal cells and also in the human body. By adding other definite ions or salts this toxic action can be obviated. Solutions which contain definite salts in such proportionate amounts that all toxic effects are lacking, in the form of colloidal injury,

which each of these salts dissolved by itself would unfold, were termed physiologically equilibrated solutions by J. Loeb. Such optimal equilibrated salt-solutions are the serum of animal blood and tissues, plant juices and sea-water.

Keining and Hopf utilized these empirical facts when they attempted to remove the toxic action of common salt by adding other salts to it, and in this way to produce, in a sense, a physiologically equilibrated salt mixture, which possesses the advantageous properties of common salt as a taste corrective but lacks its poisonous qualities.

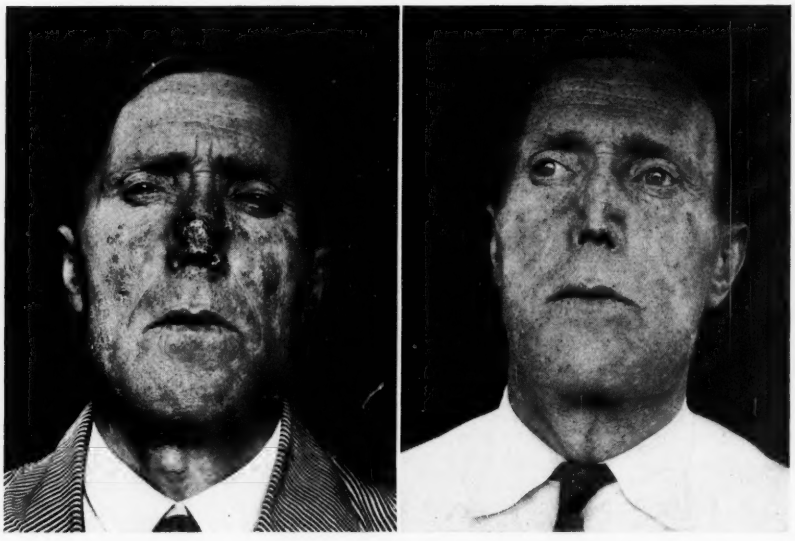


FIG. 1 FIG. 2

FIG. 1. OCTOBER 2, 1930: LUPUS VULGARIS, PARTLY ULCERATED
FIG. 2. SAME PATIENT AFTER 8½ MONTHS' DIETARY TREATMENT

I have tried this salt mixture on a number of lupus patients and achieved the same successful results with it as with the diet to which no common salt is added (see figures 1 and 2, showing a lupus patient treated in this manner). The diet was prepared precisely as directed by Sauerbruch and Herrmannsdorfer, except that the food was salted with the equilibrated salt mixture of Keining and Hopf instead of being prepared without common salt. That this modification materially simplifies and facilitates the diet is obvious.

But whether one prefers to prepare the foods without common salt or

with the salt mixture, the fact that tuberculous skin foci, including the obstinate forms of lupus vulgaris, heal under a special diet without any other treatment, is surely very impressive and remarkable. The rôle of nutrition in human disease and convalescence thereby receives renewed and special prominence.

SUMMARY

1. The diet recommended by Sauerbruch and Herrmannsdorfer for the treatment of tuberculosis, on the basis of their own researches and Gerson's previous labors, was introduced by the author, in 1928, in the Giessen Lupus Sanatorium and there tried on a large number of skin tuberculosis patients.

2. Under the influence of this diet, as the sole treatment, tuberculous skin foci heal completely. The clinical observations during all stages of the involution, particularly in lupus vulgaris, are described.

3. On the strength of these observations, the diet's chief action is regarded as an influence on the vascular system—the vascular wall cells. These have their normal function restored by the diet. All other curative processes are sequelae to the restoration of vascular function in the inflammatory region. In this process salt regulation, by salt withdrawal, and vitamine-intake support each other in their action on the vascular wall cells.

4. Keining and Hopf have obviously succeeded in solving the problem of salt regulation in another way than by omitting common salt. Salt is detoxicated by addition of other salts and thus rendered harmless. A physiologically equilibrated salt is employed, which shows successful results also in lupus vulgaris. Its use materially simplifies and facilitates the diet.

ENGINEERING CONSULTING SERVICE FOR ROENTGENOLOGISTS

During the past few years the National Tuberculosis Association has provided funds to the University of Pennsylvania for the investigation of problems concerned with radiographic apparatus and technique. The work has been under the direction of Dr. F. M. McPhedran of the Henry Phipps Institute and Professor Charles Weyl of the Moore School of Electrical Engineering.

An attempt has been made to reply by letter to requests for information received at the laboratory. It has, however, become apparent that personal consultation between engineer and roentgenologist provides the only effective means for advising the latter concerning the problems involved in the purchase and use of X-ray equipment.

Therefore, it has been decided to offer a consulting service to members of the American Sanatorium Association.

This service will make it possible for roentgenologists to obtain, as visiting consultants, the electrical engineer associated with the laboratory. These engineers are familiar with tne problems connected with the purchase and use of radiographic equipment from the points of view of roentgenologist, engineer and manufacturer.

A nominal charge in excess of travelling expenses will be made for these services. The funds derived in this manner will be applied entirely to the support of the laboratory. By this means, it is hoped that the National Tuberculosis Association may be relieved of a part of the financial burden involved in continuing the fundamental studies of technique and standardization now in progress at the University of Pennsylvania.

Detailed information concerning this projected service may be obtained by addressing: S. Reid Warren, Jr., Moore School of Electrical Engineering, University of Pennsylvania, 200 South 33rd Street, Philadelphia, Penna.

ALCOHOL AND TUBERCULOSIS

LAWRASON BROWN AND JOSEPH T. EAGAN

INTRODUCTION

"Alcoholics used moderately," wrote Austin Flint,

> entered into the treatment in most of the fatal cases. That they were more or less useful, I do not doubt, but not in the sense of exerting a special influence upon the disease. As regards their usefulness, I would place them in the category with tonic remedies, such as quinia in small, or moderate doses, and the chalybeates. . . . . Alcoholics, however, taken largely appear sometimes to exert an influence upon the disease which is remarkable.

He writes in another place,

> Alcoholics, used, not moderately or sparingly, but freely, that is, from six ounces to a pint of spirit daily—entered into the treatment of fifteen cases of which two recovered, three died, and five were untraced.
> Of the usefulness of alcoholics (he continues further on) given in considerable or large quantity, my studies have furnished striking examples. The instances of recovery, arrest, and slow progress of the disease and tolerance under their use, are too marked and numerous to be accounted for as mere coincidences. Not only, however, are they not always signally useful, but their usefulness is limited to certain proportions of cases. So far as I can judge from my experience, they are useful in the cases only in which they can be taken considerably or largely without alcoholic excitation, or any immediate unpleasant effects. There is a marked difference among phthisical patients in this regard. Some are in nowise immediately affected otherwise than that a sense of well-being is induced, and they may tolerate a much larger quantity than they were able in health. Others are either excited, or flushed, rendered unpleasantly dull, or in some way made uncomfortable. In the former class of cases, benefit may be looked for; in the latter class it is not to be expected.

The appropriateness for each patient must be determined experimentally, the quantity and the form also thus determined. They are best taken at or near meal times but they may be permitted at other times especially at bed time. "I take this occasion," he states,

to repeat a statement which I have repeatedly made heretofore, namely:—among the great number of cases in which I have advised alcoholics to be taken as a therapeutic measure in cases of phthisis, I have never known of a single instance of a patient becoming addicted to their use. As a rule patients are glad to discontinue their use when it is considered judicious to do so. On this point I desire to be understood as speaking deliberately and emphatically. . . . In these remarks on alcoholics I here had reference to their use in considerable quantity. It is only when thus used that they are to be considered as constituting a potential remedy. Given in small or moderate quantity, they entered into the treatment of a very large proportion of my cases in hospital and private practice. I have not undertaken to analyze the cases with reference to the influence of alcoholics as thus used; but I cannot doubt their usefulness, as accessory to an analeptic, restorative or supporting plan of treatment. If they improve appetite and promote assimilation, they must be useful, and they often seem to have these effects. Aside from these effects, they may operate, measureably, in the same unknown mode in which, in a considerable or large quantity, they are, in certain cases so signally useful.

Born in Pertersham, Massachusetts; a teacher in Buffalo, in Chicago, in Louisville, in New Orleans, and in New York; a profound student of physical diagnosis of the chest, Austin Flint published in 1875 one of the best books on clinical tuberculosis that has ever appeared in America. Few have dared to speak as frankly of the use of alcohol. Flint had strong backing at this time, for both Brehmer and later Dettweiler, founders of the sanatorium plan for treatment for pulmonary tuberculosis, strongly advocated alcohol, a daily bottle of wine, reinforced by stiff drinks of brandy, in the treatment of the disease. Jaccoud, long an authority on pulmonary tuberculosis in France, strongly recommended alcohol in its treatment. Mircoli held a little later that alcohol had an antitoxic action on tuberculosis and that it aided in the formation of sclerosis. Gervino, from a study of the protracted administration of small amounts of alcohol upon two tuberculous and four control rabbits, confirmed the cheering and stimulating effect of alcohol. Thomas Harris, in London, quoted by Ransome, gave 26 patients with pulmonary tuberculosis whisky for nine months, beginning with two drachms and increasing to one and a half ounces, every four hours day and night. For some the dose was too large, as the patients slept much of the day and night. But no case left the hospital worse; no case had any change in the physical signs; no case was cured.

"It was formerly thought," writes Osler,

that alcohol was in some way antagonistic to tuberculous disease but observation of late years indicates clearly that the reverse is the case and that chronic drinkers are more liable both to acute and pulmonary tuberculosis. It is probably altogether a question of altered tissue-soil, the alcohol lowering the vitality and enabling the bacillus the more readily to grow and develop.

Acute tuberculosis is very common as a terminal infection in alcoholic cirrhosis of the liver. Lancereaux thought that pulmonary tuberculosis in drinkers had special characteristics of location and evolution, in that it more frequently attacked the left apex and ran a more acute course. Fowler and Godlee stated that patients who had been addicted to alcoholic excesses suffer when attacked with tuberculosis far more severely, chiefly from loss of appetite; inability to digest food and a very irritable cough were more noticeable than in those who had led a temperate life. Samuel West held that when pulmonary tuberculosis attacked an alcoholic person it ran a more acute course, and he said that the experience with alcoholic peripheral neuritis rendered it not unlikely that the liability to phthisis was actually increased in alcoholism. He stated that alcohol did not produce cirrhotic changes in the lung. James Barr in 1905 concluded that "Alcohol has a predisposing effect to all forms of tuberculous disease, it lessens the resistance of the patient to the toxic effect of the bacilli, weakens the cardiac muscle, impairs assimilation and nutrition, and hastens protein destruction." It also leads to bronchial and laryngeal catarrh and hastens the demise of the patient. Wolff as late as 1906 thought that reliable statistics on the effect of alcohol on the causation of tuberculosis are few in number. Women and children are rarely addicted to the use of alcohol, but frequently suffer from tuberculosis. From a study of a number of cases he concluded that in only about 2.4 per cent could alcohol be considered with any degree of probability to be the cause of the outbreak of the disease. Indirectly, however, its importance could not be exaggerated. Alcohol, he thought, should be greatly restricted or forbidden for nervous and excitable consumptives and for those with a tendency to haemoptysis, especially where there is a history of previous excesses. The alcoholic treatment of Brehmer and Dettweiler has been abandoned; but, since its harmlessness in moderate doses has been proved, its use in the symptomatic treatment is justifiable. Nor should it be denied, he believed, under certain conditions as a means of enjoyment.

From this sketchy and very brief review of some of the literature con-

cerning tuberculosis and alcohol it is easy to see in what direction the medical profession was drifting; and it was thought wise to study more fully the older and more recent works upon the subject. It has been considered best to group the various references to the literature under the heads of the countries in which the observations were made. The work in Germany and France will be discussed under one section.

IN CONTINENTAL EUROPE

Brehmer, who states that he introduced alcohol into the treatment of pulmonary tuberculosis, held that it was a sparer of protein and stimulant of the appetite; that it increased, in small doses, digestion in the stomach, as well as increased fat retention; tended slightly to lower the temperature; and exerted a stimulating action on the heart and central nervous system (psychic), and a favorable influence on night-sweats and insomnia. For these reasons he held it to be a favorable drug for many patients. His followers used it in such quantities that he was forced to state that its use was no essential but only an accessory part of his treatment. Beer was no drink for patients with pulmonary tuberculosis, wine was to be used only in small quantities—about 1/3 of a litre. Opposed as always to Dettweiler, he criticized severely the amount Dettweiler recommended for daily consumption to his patients,—enough, as Cornet says, to keep them in a state of mild exhilaration. Brehmer insisted that wine should be taken as a medicament for the disease, not for pleasure. Hungarian wine, on account of the high percentage of its phosphates of lime and magnesium, was recommended above all others. Brehmer also used cognac, two teaspoonfuls in a glass of milk for night-sweats.

When Brehmer thought that it was necessary to call attention to the fact that alcohol was not an essential part of his treatment but only an accessory, it is entirely possible that he had Dettweiler in mind. "I repeat again," wrote Brehmer's old assistant, Dettweiler,

> that a flask of good Rhine or Bordeaux wine and seventy to eighty grams of cognac daily on an average in broken doses aids the *Phthisiker* and never harms him. In those not accustomed to wine, I begin with the smallest quantity, tolerance increases every day, it changes to a demand, which is instinctively felt on account of the beneficial action on the weakened organism. Alcohol is a means of nourishment, a means of medication, a means of pleasure, truly a triad of qualities that it is not easy to find united in any other one substance.

After reviewing some of the pharmacological work of the time he goes on to say that "we stick too much to the old tradition that all healing agents must come from a pharmacy. The dose must be regulated in regard to amount and time." He apparently clung to the old idea that wine increased the amount of blood in the body on account of the increased warmth of the skin, which we to-day know is due only to the change in the distribution of the blood. He subjected all his patients to such treatment and only with "good results." He usually followed such treatment only for a few weeks but did not hesitate to use it when necessary from time to time.

Espina Y. Capo, in 1905, in his article *Alcohol et tuberculose* concludes that alcoholism and tuberculosis together constitute the worst disease combination, for every alcoholic is a candidate for tuberculosis. Early arteriosclerosis (hardening of the arteries) of the alcoholic and of the tuberculous individual is identical in its histological structure with senile arteriosclerosis. Tuberculosis has only one coefficient of incurability, namely, alcohol, which makes it completely incurable. If one wishes to obtain results in the antituberculosis battle, it is necessary to unite in a common action the effects of antialcoholic and antituberculosis leagues.

Abadie and Grenier de Cardenal at the same Congress (1905) said that all hygienists and pathologists to-day consider alcoholism a factor of highest importance in the aetiology of tuberculosis. They verified this fact by a study among the poorer working classes. This was made with the greatest care and applied to all of the cases of pleuropulmonary tuberculosis hospitalized in the Hospital Saint André de Bordeaux from August 1 to September 15, 1905. They noted in more than half of the cases (56.8 per cent) in the past history (pathological or social) of the invalids, the habit of prolonged use of alcoholic drink. The man, who tipples more often than the woman, should as a result of this vice contract tuberculosis earlier. Tuberculosis of adult age or at the beginning of old age appears often as the result of alcoholic intoxication, sometimes as the result of small doses long continued. The adolescent or young man who indulges in alcohol rapidly becomes tuberculous. The children of tuberculous parents have a tendency to develop tuberculosis in adolescence. The habits of the husband have an undoubted influence on the tuberculization of the woman, whether it is because the drinking husband becomes tuberculous and creates a conjugal focus of infection or because the vice of the husband brings about want in the household, overwork and priva-

tions of the woman and thus, secondarily, induces tuberculosis in her. The result of their research confirmed the view that the antialcoholic battle was to be considered the basis of prophylaxis of tuberculosis.

Achard and Gaillard (1905) first of all quoted Roos, who found that in guinea pigs alcoholization by wine mixed with the food did not make worse or modify the course of tuberculosis. The average life of three sets of alcoholized guinea pigs was ninety-four days and that of three sets of controls was ninety-five days. These authors (Achard and Gaillard) used 60 guinea pigs, all of which were inoculated the same day with human tubercle bacilli. The results led them to conclude that alcoholic intoxication, brought about repeatedly by whatever method of entrance (skin, stomach, or lungs), hastened the course of experimental tuberculosis.

Cornet (1907) stated that opinion in regard to the predisposing effect of alcohol to tuberculosis was still divided. James Clark, Richardson and Mackenzie of England, Launay, Lancereaux, Fournier, Legrain of France, Strümpell, Bollinger and Mosler of Germany, all held that alcohol predisposed to tuberculosis. Cornet quoted Baer's figures to show that those connected with the manufacture and sale of alcoholics are more disposed to contract tuberculosis, and mentions that Laverenne thought the figures of alcoholic consumption and the mortality rate from tuberculosis closely agreed in the different departments of France. Laitinen, Achard and Gaillard all thought that alcohol increased the susceptibility to artificial infection. Some hold that the offspring of alcoholics are more susceptible to tuberculosis (Forster and Pegurier, and Bunge) but this is denied by others (Meyerhoff, Peters, Jackson, Leudet). Cornet recalled that Dettweiller healed some of his patients while they were in a state of mild alcoholic excitement. He states, however, that alcohol weakens the expulsive action of the ciliated cells, whereby the inspired bacteria are often expelled, and recalls the splendid work of Bollinger who showed that alcohol weakens the heart. How far alcohol consumed in the body affects the growth of the tubercle bacillus no one can say; but the bad air and late hours that often accompany drinking may weaken the bodily resistance to the bacillus. Unfortunately there are no figures upon most of these points to allow us to draw definite conclusions. Cornet recommended a glass of light wine with meals or with an egg between meals. Beer or porter at bedtime may induce sleep. Cognac (one or two teaspoonsful in a glass of milk) may prevent night-sweats. Alcohol should be considered a whip for the heart, and should be used thoughtfully and never for at least a week after an haemoptysis.

Bandelier and Roepke in their *Clinical System of Tuberculosis* (1913) hold a middle path and say that alcohol is not necessary for the patient, but also that it is not harmful. There is no compelling reason to make tuberculosis patients abstainers. A glass of beer or light table wine should be allowed at the principal meals to those who eat better with it. No harm is attendant upon it; rather it is favorable, as such beverages increase the secretion of digestive juice.

Hollos in 1912 was struck by the fact that the same tuberculous individuals who show no symptoms of intoxication following infection possess no immunity to tuberculosis. In a great number of cases these are descended from parents (especially a father) whose alcoholism is established. Familial infection encountered here a posterity that had developed out of semen and ova weakened by alcohol, and therefore the capacity for attempts at immunization had little or no degree of success. In the latent stage of sickness this defect showed itself in the weak development of the organism and later, when the disease became manifest, the condition from the beginning of the manifestation was virulent, of rapid course, and fatal.

In 1912, Ewald, writing of alcohol and infectious diseases, says that experimenters are agreed that alcohol has a harmful influence on the course and development of the infectious diseases. The natural defenses of the body are depressed, blood-pressure and respiration are affected adversely and the slight antipyretic and albumen-sparing action of alcohol are by comparison negligible. This applies to tuberculosis also.

Kamnew-Schuja (1912) is of the opinion that small amounts of alcohol are not harmful to the tuberculous. As an example he mentions the use of koumiss in the treatment of pulmonary tuberculous. This contains from 2.23 to 2.75 per cent of alcohol and some sick people average an intake of about three litres daily. This amounts to 75 gm. of alcohol daily. The good results of the treatment are widely recognized.

Holitscher, in 1913, writing on *Alkoholismus und Tuberkulose*, gave the results of a study of 2,730 questionnaires collected from patients in Norway, Sweden and Hungary. He found 22.2 per cent intemperates in poorhouses. He then considered the individual classes by themselves, and found in the age-group 16 to 25 (827 cases) that 95 per cent of the invalids were moderate and only 5 per cent intemperate. In the next age-group, 26 to 35 (728 cases), he found 79.5 per cent moderate and 20.5 per cent immoderate. In the age-group, 35 to 45 (393 cases), the figures were 61 per cent moderate and 39 per cent immoderate (or intemperate). In the

age-group over 45 years the intemperates preponderated by far and, too, the number of frank topers became noteworthily great. Of 150 in age-group 46 to 55 years, the analysis showed that two-thirds were doubtlessly under the influence of alcohol. The figures for those over 56 years were too small to be free from objection. There were only 69 cases of which a little over one-third were moderate and over two-thirds (71 per cent) immoderate.

The conclusions from the above figures are that among young tuberculous patients there are many fewer drinkers than would correspond to the average of the population and that with increasing age the ratio shifts, so that among consumptives of higher age a very surprisingly large percentage of alcoholics can be established. He explains this on the supposition that the tuberculous infection of a young organism calls forth an antipathy to alcohol. Otherwise are the relations in the higher age-groups: indeed here heredity plays a great rôle; moreover, the influence of alcohol shows off to advantage from decade to decade. The formula, he concludes, is that *the tuberculous are for the most part not alcoholics; but alcoholics run the danger of becoming tuberculous.*

Holitscher next considers the hereditary taint chiefly of those with tuberculosis. He found an average hereditary taint of almost 50 per cent (partly explained by the fact that younger people are able to give more exact information about sicknesses of which their parents died). He then investigated how great the taint was in the immoderate and moderate groups. The ratio among the moderates was higher and among the intemperates (immoderates) lower than the general average: the former about 21 to 37 per cent, in general 25 per cent, more afflicted than the latter. A history of drunkenness of the father was given by 319 people. In the series of the temperates the percentage was about 15 and in the immoderates (intemperates) significantly greater,—from 27 to 29 per cent. More than a fourth of all invalids came from a family in which there was drunkenness. They, therefore, had inherited tuberculosis and alcoholism.

Among the women Holitscher noted that alcohol played a rôle of diminishing importance as an aetiological factor in tuberculosis. He observed that the hereditary taint among females appeared in a significantly higher percentage than in males and especially in higher age-groups. This means that among the women in whom a decrease of resistance occurs as a result of drink, particularly in old age, only such die of tuberculosis as inherit the predisposition or in whom the opportunity for repeated in-

fection was especially great (as by nursing a sick spouse). The strengthening of his conclusions is seen in that the number of cases of sick and dead generally and of tuberculosis in particular, among women in the higher age-groups, especially in similar vocations, is essentially lower than among men.

Finally, exact figures are impossible to obtain but he postulates that the highest average misuse of alcohol is to be found in men of the so called best years of life (26 to 35). No one will be able to assert that among men over 46 there are more than two-thirds of heavy drinkers when, according to the same standard, there are only one-fifth between 26 and 35. Much more obvious would it be if the ratio had been reversed. This objection is therefore untenable, and the finding remains undisputed that very many drinkers in higher age-groups fall victims to tuberculosis as a result of reduction of their resistance to tuberculosis by alcohol.

Orth (1915) says that alcohol is only a contributing factor in so far as it influences dwelling-misery and poor nourishment. There is no definite proof that the frequency of the deaths and that of the use of spirits coincide, nor is it proved that the male is more affected by tuberculosis than the female sex because of alcohol. Writing of alcoholism and tuberculosis (1916), he says, "Rather does not much speak for the contrary that alcohol not only does not harm but that alcoholics are more favorably constituted against tuberculosis than temperate people. It is at variance with the widespread view of the day, but one has only to think of Dettweiler to agree that the tuberculous suffered no demonstrable harm from alcohol."

Since the cause of tuberculosis, says Lilienthal in 1915, was found toward the end of the 19th century by Robert Koch, alcohol can be designated only a contributory cause. However, there is some controversy about its effects on the course of tuberculosis, some asserting that it prolongs and others that it hastens the disease. Orth quotes in support of the opinion that it prolongs tuberculosis, that the deceased coroner Baer observed that pulmonary tuberculosis was infrequent among the topers of the present population, and that when present it ran a slow course. If one bears in mind the fact that abstinence is enforced during jail terms, the fact that Baer observed tuberculosis relatively seldom among the alcoholics who constituted about 25 per cent of the imprisoned, is misleading. So also is the great variation in statistical findings of poor-houses and sanatoria. As to how many alcoholics suffer from tuberculosis and also as to how many alcoholics are present among the

tuberculous, one finds that it varies from 1.8 to 90.5 per cent. Just as inconclusive for the question is the fact that, in the so called alcoholic industries and all industries that have to do with the serving or manufacture of alcoholic drinks, the mortality exceeds more or less that of the general population and that tuberculosis is one of the most frequent causes of death among such employees. Two accompaniments of alcohol, namely, poor dwellings and bad nourishment, can be adduced as predisposing agents. For the institution of an antialcoholic movement it is of no moment whether alcohol furthers the spread, that is, increases tuberculosis directly or indirectly by social misery. But for scientific purposes it is not the same. The task must be to determine whether and how far alcohol, as such, works or does not work.

Orth next investigates the question of whether the frequency of fatal tuberculosis cases and the peak of alcoholic consumption, especially brandy, as calculated for the population in general, parallel each other. Bertillon recorded this in 1900, showing the brandy consumption and tuberculosis mortality of the various provinces of France. If one examines these records carefully it is apparent that the parallelism is a generally superficial one, with unseemly gross fluctuation in both directions. In view of this absolutely irregular finding, it appears impossible for Orth to see a sufficient foundation for the statement that in France brandy indulgence is responsible for the appearance of pulmonary tuberculosis; nor does he draw any conclusions, as he does not regard brandy consumption an index for chronic alcoholism.

Another proof of the significance of alcohol with respect to tuberculosis is seen in the fact that the male sex is more affected with tuberculosis than the female; and of course alcoholism is more widespread among the former. The fact is definite, but the mortality of the two sexes is not parallel and especially in the later age-decades the relationship is very variable,—sometimes indeed reversed. Orth investigated the relation of the two sexes in an official review in tables for the years 1900 to 1902 and 1910 to 1912. In the first year and often to the end of the second, and not infrequently to the end of the third year the tuberculosis mortality is greater in boys than in girls. Then the reverse changes start; and at the end of the twentieth year many more females than males have died of tuberculosis. Indeed, the absolute mortality of women is 14 to 15 per cent greater than that of the males. It is noteworthy that in 1912 both sexes showed a drop in mortality that was more marked among

women than men. The development of the abstinence movement among youths cannot be held to explain this.

Between the twentieth and thirtieth years the absolute mortality of tuberculosis is especially high, for it is only a little less than the total combined mortality for the first twenty years. Even in this period there is some drop in the mortality; however, in the last three years it is insignificant among the women and nil among the men. In fact, in the last years the figures for men are even higher. It is especially noteworthy that in the two compared peroids, which extend over a decade, the relationship of the mortality of men to women is reversed. But, despite the preponderance of male mortality in this decade during the first period of this comparison, the total mortality of males for the first thirty years is less than that of women, even if the difference is less than it is a decade later. The sex mortality between thirty and forty years is similar. The situation of the absolute mortality after the fortieth year is otherwise. During that time many more men than women die of tuberculosis and indeed more than in both periods of comparison. The same results are obtained from comparison of the relative numbers of tuberculosis deaths in every 10,000 of the general population and the totality of each sex for the years 1901 to 1902 and 1911 and 1912, calculated upon the 10,000 living, in the age-groups under discussion, and on 100 deaths of the classes under discussion. If one remembers that in recent years about two-thirds of all tuberculosis deaths occur in the first forty years, then one cannot admit that alcoholism of men is a big factor, inasmuch as female deaths exceed. It is otherwise, however, with the last one-third of the tuberculosis deaths which concern the population above forty. Here the male sex predominates, even if the difference in the last years is smaller. To attribute to alcohol this preponderance of the male sex and the relatively sharper drop of mortality as a consequence of the temperance movement, Orth considers a prejudiced opinion. Orth himself attributes the relative drop to improved industrial hygiene, inasmuch as the abstinence movement rather weans away younger people from drink than makes old topers renounce drink. In the older ages the number of tuberculosis deaths has regularly receded, but not so the infant mortality from tuberculosis. Then too experimental work does not bespeak a direct connection between alcohol and tuberculosis. Here arise two questions: (1) whether continued alcoholism favors the implantation of the infection and (2) whether the course of tuberculosis is unfavorably influenced by alcohol. Here too one encounters the contra-

dictory findings of various investigators. Orth injected alcohol subcutaneously, since injection into the blood is a very radical method and is poorly adapted for long-continued work, and since overfeeding results in gastric disturbances which give uncertain results. Injections were given into rabbits, and in general were well borne. The rabbits were injected with doses corresponding to intoxicating doses in men, and infection was induced by both human and bovine types of bacilli. After the animals had taken their allowance for four weeks this was continued for four weeks longer. In one injected with autopsy material, dying after twenty-nine weeks of an intestinal infection, there was found at the site of inoculation a pea-sized tuberculous nodule. The bovine strain was isolated from the lungs of a cow. The work resulted as follows: The alcoholization of rabbits done by Orth did not increase the effect of a slighly virulent strain of tubercle bacilli. The results with the human type were similar. The animals had only a local sharply circumscribed change, indistinguishable in the control as compared with the alcoholized animals. Despite the small numbers (six rabbits with human and four with bovine bacilli), one may conclude that under the conditions of Orth's experiment no effect of alcohol promoting an increased progress of the tuberculosis was to be seen. Orth, however, does not take up arms in defense of alcohol; he only maintains that the battle against alcohol, which he considers a dangerous enemy of humanity, must be placed on a firm scientific basis.

Holitscher in 1916 stated that a controversy existed in the literature over the connection between tuberculosis and alcohol. Differences in and the use of the material explain this. Young people are temperate and alcohol is a negligible factor in them. Among the old tuberculous are more heavy drinkers than are found in the average population. The author declared that those predisposed by heredity and those infected in childhood, for reasons physical or psychical, inherent to changes in organism due to tuberculosis, have no urge to use alcohol. On the contrary, many drinkers die in later years as a result of a decrease in bodily resistance against this infection. Experience, therefore, teaches us that the tuberculous who are phthisically affected are seldom drinkers; and, on the contrary, the danger that alcoholics may become tuberculous is very great.

Mouisset, in 1922, mentioned that alcohol predisposes to tuberculosis and favors its advance by lessening the resistance of the body and causing digestive disturbances, and by producing derangement of the nervous

apparatus. The misuse of alcohol may increase cough, shortness of breath, and digestive disturbances, symptoms which after a time, as a result of abstinence, completely disappear. The relationship between cirrhosis of liver, tuberculosis and alcohol was brought out. It is striking that in cirrhotics tuberculosis often develops, but the process in the lung does not become extensive and death occurs, not as a result of tuberculosis, but of a liver disorder. There is a form of cirrhosis (tuberculous), but this remains latent if there is no alcoholism. Alcohol does not have a harmful influence in every case of tuberculosis, and in some cases it may favor sclerosis. This favorable action is not seen in young individuals nor in those in whom alcohol causes loss of appetite and digestive disturbances.

Gerwiener, in 1922, wrote that, as contrasted to numerous antipyretics, alcohol, in the meaning of the original Brehmer-Dettweiler scheme, acts as a febrifuge, and that especially in subfebrile temperature it offers a great advantage because it at once acts as a favorable stimulus to the weak heart of the tuberculous. The prompt effect of the well-known hypnotic of Brehmer is also known. This consisted of a glass of cold milk with good cognac, for the diminution if not the cure of night-sweats. A more significant advantage is that alcohol affords nourishment after quick absorption. Also in pulmonary haemorrhages alcohol is preferable to the group of styptics which in cases of parenchymatous bleeding, even earlier, might harm. It is unnecessary to warn that alcohol is not a panacea, but as tuberculous patients, more than other patients, need direct stimulation and incitement, it would be a misdeed to deny such a patient alcohol, which increases bodily and muscular power,—alcohol which also is therapeutically favorable for the disease and nourishing as well.

Seiffert (1922) says that the results gained from a study of 835 histories of alcoholics showed only 6.48 per cent to have definite signs of tuberculosis, and of these only four were advancing cases. It also appeared that, at least at the onset, alcoholics were in no way worse equipped to fight the battle against tuberculosis than were other people. In addition, the vast majority of the inmates of the institution showed changes attributable to a lessening of the lung elasticity, ranging from slight and scarcely demonstrable disturbances to outspoken emphysema and bronchial catarrh. Observations on the ergostat showed that the rate of breathing in drunken individuals, on the average, was higher than the rate of breathing of healthy adults, a result of the general muscular atony which

also affected the respiratory muscles, because deep vigorous breaths were taboo, and also because of emphysema.

Samson, in 1924, writes, "Is the influence of chronic alcoholic use on the origin and course of tuberculosis unequivocally a direct one or are there other contributing factors alongside of which alcohol is accidental?" Also, might there not also be an indirect equivocal connection with tuberculosis? These questions cannot be settled experimentally because of the impossibility of comparing results in animals with those in man. Statistics on living men are too diverse and too complicated by social factors, so that the true effect of alcohol cannot be segragated from that of other factors. According to Kursteiners, in the so called alcoholic pursuits (innkeeper, cooper) the tuberculosis mortality in the higher age-groups is small as compared to the younger groups if the business itself is not injurious. In other trades unrelated to alcohol, we find a high mortality; as, for example, among confectioners and coffee-roasters, with 30.9 per cent calculated on 100 deaths; clock and watch-makers with 30 per cent; and building and machine locksmiths with 28 per cent; stone-cutters with 28.3 per cent. All of these exceed the innkeepers' mortality of 22.3 per cent and the average of 14.4 per cent of all dying of pulmonary tuberculosis. Koelsch found the average mortality from tuberculosis among 1,000 women to be 4.07 per cent; maids and cooks 13.8 per cent and charwomen 34.9 per cent, all of these exceeding the average; while barmaids had 1.60 per cent, which was almost the lowest. General unhygienic living conditions and vocational influences have added to them a kind of vocation-selection in the sense that an influx of weak and half-invalided persons to this vocation lends it a certain inferiority. Hence, there is high morbidity and mortality and, at the same time, a high tuberculosis mortality. Therefore alcohol alone cannot be considered a cause for the high tuberculosis mortality. Some indirect equivocal influence can be attributed to alcohol, however, as indicated by Henschen and designated "alcoholism-pauperism." Hence, research on human material is desirable, so as, first of all, to have a sufficiently large number of alcoholics as a foundation for general conclusions; second, to have a certain social medical comparison in respect to general and special industrial dangers and sicknesses; and, third, the chief claim to be fulfilled, namely, that, through defective nutrition during the stresses of labor, the effect of alcohol be not entirely lost sight of. These three requisites I found in an approximately perfect way pertinent to the Berlin "public girls" with reference to whom I arrived at surprising results after years

of research on tuberculosis. These female drinkers are divided into three groups,—moderate, heavy and very heavy imbibers. Included in 1,300 *puellae publicae* were 29.1 per cent drinkers. (P. P.). According to the Turban-Gerhardt classification, 17.2 per cent of these women drinkers have a part in the tuberculosis morbidity as contrasted with 25.4 per cent of the abstainers. With respect to the individual stages, stage 2 with 28.8 per cent among alcoholics as contrasted with 20.2 per cent of abstainers and stage 3 with 4.5 per cent among alcoholics as contrasted with 3 per cent of abstainers contribute a greater part to the whole of tuberculosis cases. Another table shows that among the healthy a greater number of drinkers (31.8 per cent) is present than among the tuberculous (22.1 per cent). Indeed, the more pronounced the abuse of alcohol, the less participation in tuberculosis. Drinkers of the first and second grades are tuberculous less often than the healthy, but the heaviest drinkers of grade 3 overbalance the healthy (41.9 per cent to 28.3 per cent). Summarizing, we find first that, by and large, tuberculosis is less frequent among alcohol-drinkers than among abstainers; and, second, that among drinkers with tuberculosis the advanced stages of illness occur more frequently. The explanation for point 2 is not unequivocal and both possibilities are here given with reservation. One may say that female drinkers fundamentally possess a resistant constitution and this manifests itself in a prolonged course of the tuberculosis. One must also remember that alcoholism, as such, might neutralize the advance of the tuberculosis, a concept which Orth in his autopsy records, shortly to be mentioned, has supported.

From further study Samson derives two known possibilities. At the same time it is plain that alcoholics (women) by and large die in fewer numbers of tuberculosis than do abstainers. J. Orth has autopsied 218 heavy drinkers in the course of ten years, with especial reference to pulmonary tuberculosis. His numbers led him to conclude that the greater the fondness for drink the more prompt the cessation of the decline and healing of the tuberculous spots. Orth concludes that alcohol is not only not harmful but that alcoholics are more resistant to tuberculosis than are abstainers. Bertholet at the Pathological Institute of the University of Lausanne found, in 163 autopsies of alcoholics, 32 per cent with tuberculous infection, and in 100 abstainers 33 per cent with such infection.

During war-time, deaths from alcohol decreased but those due to tuberculosis did not. Then, too, Pfeideron's graphic presentation of experimental results which Walter Kern has arranged (having to do with inocu-

lation of tubercle bacilli into guinea pigs) are the less convincing the more exactly one scrutinizes the original protocols. If we maintain that neither animal experiment nor human pathologicoanatomical and clinical observations have given proof that alcohol causes a direct and immediate increase of tuberculosis mortality, nevertheless we must expressly add that the manifold consequences of the misuse of alcohol, threatening health and life, are by no means lessened by these findings given above.

In 1925 Arnould answered the alcohol question negatively and supported himself essentially by researches of French and English origin and also from other sources. He maintained that most cases of tuberculosis arise at an age-period at which alcoholism is not common. On the other hand, the use of alcohol is greatest between the years thirty to sixty (in both sexes), while tuberculosis is least frequent at these times. In the past thirteen years in England and Germany alcoholic abuse has been the same while tuberculosis mortality has been halved. Particularly in France one observes that alcohol consumption in some places is greater in the country and again in other localities in the city, but the tuberculosis mortality is always less in the country. The greater the population in the cities the less the misuse of alcohol but so much the greater is the tuberculosis mortality. These statistical results, Arnould maintained, correspond to clinical and experimental experience.

The same author (1923) disregarded preconceived and often-repeated ideas with respect to the relations of alcohol and tuberculosis, and concluded that the averages of the official statistics for the years 1907 to 1913, inclusive, proved that the rate of tuberculosis mortality is higher the higher the population, and at the same time the rate of alcohol consumption is lower. During the period studied (seven years) the rate of alcohol used per person increased progressively a little in all of the cities and in the rural districts as well, while the rate of tuberculosis mortality showed a steady decline. He was forced to consider that the opinion, so widespread as to the relation between alcohol and tuberculosis, was entirely erroneous. In brief, he said that the statistics studied by him "in no way establish any appreciable parallelism, either in extent or time, between alcoholism and tuberculosis."

Kolber stated in 1925 that the relation between alcohol and tuberculosis is not simple. The majority of deaths from tuberculosis occur at an age when alcoholism is not yet frequent. In addition, not many fewer women than men die of tuberculosis although in general they are less often addicted to alcohol. Many difficulties arise in attempting to com-

prehend these matters statistically. The statistics which concern alcoholic consumption in the separate walks of life are significant, and they reveal that in the so called "alcoholic vocations" tuberculosis mortality is greater than in the remaining cross-section of the population.

Schemitz in 1928 brought out some interesting facts. He claimed that there exists a close connection between tuberculosis and alcohol, but, on the other hand, that there is no relation between wine production and tuberculosis; and he cited as evidence that tuberculosis is more widespread in countries where spirits are distilled than in the wine-producing countries. He considered it remarkable that Germany and Hungary belong to the countries which do not carry on wine-growing. In Italy, tuberculosis in the North, where no wine and more spirits are used, is more widespread than in the South where wine is abundant. He thought small quantities of wine not harmful, particularly at meal-time.

Bandel in 1929 says that the known greater share of the female sex in the tuberculosis mortality during the World War affected strikingly also the neutral foreign countries, such as Denmark and Switzerland, so that the increased demands of work made on the women of Germany could not have been the cause of this increase. Additional evidence comes from the fact that, not the ages twenty to forty, but those from forty to sixty years showed the greatest incidence. The specific male mortality in tuberculosis is, up to 1919, more favorable, but from 1920 on again more unfavorable than the mortality of women. It is in the age-range from forty to fifty years during 1919–1920 almost 50 per cent lower than in 1910. Besides, the total mortality of the mentioned age-periods is lowered in Germany as well as in the neutral states. All of these countries had at that time something in common, namely, a decrease in alcohol production. While, therefore, a scarcity of food evoked a general increase in tuberculosis mortality, alcohol scarcity has for the greater part compensated in men the damages of war. Hence, Bandel concluded, an influence on tuberculosis mortality by alcohol cannot be denied.

Summarizing, the introduction of alcohol into the therapeutic treatment of pulmonary tuberculosis was due, as he himself stated, to Brehmer, the pioneer of sanatorium treatment. However, Brehmer soon felt it necessary to warn that it was not an essential but only an adjunct to sanatorium treatment. Dettweiler in all probability kept many of his patients in a state of mild exhilaration for weeks at a time. He claimed, as did Flint, that he did harm to none. Cornet called attention to the dangers associated with drinking. As time goes on we find Ban-

delier and Roepke saying that it is unnecessary but not harmful. Hollos again called attention to the lack of immunity in the offspring of alcoholics. Ewald thought it lessened resistance in the partaker. Orth combated this view, and pointed to the patients of Dettweiler as proof that his contention is correct. Lilienthal showed how easy it is to draw erroneous conclusions from the study of the effects of alcohol in tuberculosis. Holitscher concluded that those inclined toward tuberculosis are less likely to overindulge in alcohol, but that many alcoholics do become tuberculous. It seems unnecessary to answer some of the statements of Mouisset, as they will occur elsewhere. Samson questioned the conclusions that alcohol increases susceptibility to tuberculosis and quotes figures from a study of prostitutes to show that such is not the case among them. But he by no means depreciated the danger of alcoholic misuse on health and life. Arnould called attention to the facts that the age-incidences of alcoholism and tuberculosis do not coincide, and that, even if country dwellers take more alcohol than city dwellers, their tuberculosis mortality is always lower. Kolber agreed that it is difficult to connect alcohol and tuberculosis. Schemitz would connect distilled spirits with tuberculosis, but not wine, while Bandel from an analysis of figures stated that tuberculosis mortality is affected by alcohol.

IN GREAT BRITAIN

The following abstracts of articles on the relation of alcohol to tuberculosis in Great Britain portray fairly well the attitude of many men in that country.

In 1892 George T. Congreve expresses very clearly the general medical opinion in Great Britain on the use of alcohol and says,

> Of malt liquors the only kind allowable is the bitter pale ale except good stout occasionally; half a pint may be taken once, or by persons accustomed to malt liquors, twice a day. If either of these causes flushing, increase of cough, headache or feverish heats, they must be discontinued. Spirits in general must be prohibited, being of too stimulating a nature. Not always so—there are sometimes cases in which I find that one tablespoonful of the best French brandy with half a tumblerful of water or soda water or seltzer water supplied at the dinner meal affords a gentle stimulus to the stomach, promotes the appetite and helps the digestion of food. There are cases also in which unsweetened gin (as sent out by the distillers), well diluted, may be taken at night, but there is rarely such an absolute necessity for any kind of alcohol that would cause me to offend the conscientious scruples of my teetotal friend. I have been per-

fectly astonished to hear of alcohol, especially whisky, as a great carbon producing spirit, being lauded in America as a remedy for consumption. I have been horrified to hear of patients who have been kept in a state of alcoholic excitement till hopeless brain complications have arisen. Wines, if taken at all, must be used in moderation. When no spirits are taken, a glass of good port wine, with a biscuit, may be proper once or twice a day according to circumstances. The patient may take at dinner either two glasses of good sound claret, free from acidity, or Burgundy, diluted or not, or a glass of sherry with water. The sherry should be a light dry wine; when sickness is a troublesome symptom, interfering with the retention of food, a glass of dry champagne will be proper. Should any patient be traveling or visiting abroad the wines of the country are the best and such as are free from acidity or sweetness may be admitted sparingly.

Fothergill in his *Handbook of Treatment* strongly recommended rum and milk in the morning before dressing (1895).

In the *Hygienic Prevention of Consumption* by Squire (1893) is the statement that alcohol may be taken in the form of beer or light wines if required to assist the appetite and add relish to a meal; the stronger forms of alcohol are not often necessary and should be taken only under medical orders.

Harris and Beale (1895) consider wine, such as port, preferable to spirits. If, however, the fever is high or the condition of the patient is anxious from any cause, they prefer to administer brandy or whisky. Three to six ounces of wine or four ounces of brandy in the course of the day and night will usually be found sufficient. They suggest that dry sherry, good Madeira or Marsala may be sometimes substituted for port.

Arthur Latham states in 1905 that alcoholic stimulants should be reserved for emergencies. Most patients, according to him, may be allowed a glass of beer or wine, preferably claret, with their mid-day and evening meals and the majority find no difficulty in taking either beer or claret in addition to their milk. When the temperature is elevated or the digestion is disordered both brandy and champagne are exceedingly useful. The cough, which occurs the first thing in the morning, is useful and must not be checked by a sedative. We may aid this form of cough by giving some warm drink such as milk or tea to the patient before he arises. Or, we may give a little rum and milk—a dessertspoonful of rum to a claret glass of warm milk, or we may prescribe an alkaline draught.

In 1909 F. Ryfenacht Walters wrote that stimulants are not usually

required during an out-of-door life. There are cases, however, in which a well-chosen alcoholic stimulant greatly helps the digestion of food and the patient's recovery can be hastened thereby. Except for emergencies and for quite short periods of fever and weakness not more than one and a half ounces of pure spirit should be taken *per diem*. As a rule it should be taken well diluted with food rather than on an empty stomach. It should not be taken to keep people warm, as in the long run it increases the loss of heat from the body. When a stimulant is required to stave off a chill, hot soup or hot milk or cocoa is preferable.

A. J. Jex-Blake (1915) says that a great change with respect to the use of alcohol in chronic disease has come over the medical profession in the last twenty years. He agrees that alcohol often improves the appetite and aids a weak digestion and, taken in moderate quantities for a lifetime, may seem to do nothing but good. It is also a food (though denied by many). On the other hand, it is in no way essential to the cure of tuberculosis and, if prescribed at all, should be given as a medicine and only for a definite period of time. The patient may find too easy comfort in the cup, and the temptations of chronic alcoholism in a chronic and depressing malady like tuberculosis should not be underrated. Alcohol should not be used for some time after haemoptysis and special care should be taken in cold climates and at high elevations. Nervous patients should avoid it. Individuals long accustomed to its use should cut down on their intake. It should not be prescribed in cases in which it increases cough or irritates the larynx or stomach. In brief, it may be said to be a dangerous food, a symptomatic drug of considerable potential danger but of value in some cases of pulmonary tuberculosis. A cocktail (drachm of whisky), glass of stout or of bitter ale or of good wine, taken before or, better, with the first part of a meal, may aid a flagging appetite or a weak digestion. When impossible for patients to take milk without a small amount of brandy or whisky, or eggs without sherry, these should be allowed. Insomnia may be relieved by a glass of beer or ale or a little whisky at the hour of sleep, but these are dangerous. Brandy and champagne are of value in some cases late in the disease. Judicious though rather free use of spirits does unquestionably prolong the existence of a few patents with slowly progressing chronic disease. Alcohol, as a whole, is not necessary in the treatment of pulmonary tuberculosis as the same effect can be produced more surely, if less pleasantly, by some other drug.

Brehmer considered wine as an important article in the treatment.

Hungarian wine was preferred above others because of its high percentage of phosphate of lime and of magnesium. By its alcoholic content it lessens the wasting away of consumptives and through the phosphate of lime it assists in building up the structure of the body. The use of wine was not confined to its value in the diet. It was used to combat the chills of hectic fever and to moderate resulting high fever. Cognac was also used for night-sweats.

Burrell admits, in 1929, that the question is a difficult one because the disease is chronic and the patients are subject to periods of depression so that the alcohol habit may be easily formed:

> It should not be used as readily as in acute disease where action as a food renders it valuable in helping through the crisis. Apart from the danger of habit it is good in moderation. It assists the digestion and the addition of a glass of stout or port to the diet will often turn the scale in favor of the patient. Some years ago the treatment was rum and milk and I am told that the patients thrived on it. As a general rule one would say that if patients are doing well without alcohol so much the better because of the real danger of producing a habit, and that spirits should be forbidden except in the case of elderly patients who are accustomed to them. On the other hand, one should never forget that alcohol often does good and should not be withheld under certain conditions.

Such opinions express very clearly that the use of alcohol in the treatment of tuberculosis in Great Britain has undergone great change and, except in the case of those accustomed or addicted to its use, alcohol is greatly restricted. By many it is used only in emergencies. By some, and probably the number is increasing, it is rarely if ever employed; for they hold with Jex-Blake that the desired results can be obtained more surely, even if less pleasantly, by other means.

IN AMERICA

In America opinion in regard to alcohol and tuberculosis has departed far from that expressed by Flint. Possibly due to the rapid changes of temperature, or to other climatic conditions, a nervous instability, as manifested by the "rush" of modern life throughout the continent, most pronounced in New York, and an inability to relax from a state of high tension, have rendered the use of alcohol doubly dangerous in modern American conditions.

Knopf (1899) held that it is difficult to lay down any rule on the subject of the use of alcohol in pulmonary tuberculosis. His experience has

taught that it is indispensable in some cases and that it should be given preferably in the diluted form of wine or beer or good cognac in small quantities mixed with milk. He thinks it should rarely be given as an antipyretic remedy. Cognac or whisky should be dealt out carefully, like powerful and dangerous medicines. If patients are treated in a sanatorium the real effect can be gauged during the frequent (daily) visits of the physician.

Osler (1897) thought that alcohol should not be given as a routine matter to tuberculous patients. It is often beneficial in cases with feeble digestion and high fever and in the later stages of the disease when the heart's action becomes rapid and weak. There are cases in which three or four ounces of whisky taken as milk punches, or given with egg albumen, seem to promote the appetite and improve general nutrition. Routine administration is not advisable, and there is no evidence to uphold the old idea that the persistent use of alcohol promotes fibroid changes in the tuberculous areas.

In 1901 Preble stated that in modern times the minimum physiological dose of alcohol is what is used in the treatment of tuberculosis. The physiological action of alcohol he held to be the check of nitrogenous waste, the promotion of appetite, the acceleration of digestion when given in small doses, the facilitation of fat deposit and a slight reduction of temperature. It also is believed to stimulate the heart and the nervous system and to influence favorably night-sweats and insomnia. Alcohol should be valuable if abuse is guarded against. Tolerance is the essential point. It should be prohibited to those in whom it goes against the grain, and to all children. Alcoholic beverages are best taken while eating and, if spirits are required between meals, they should be given in the form of egg-nogg or milk-punch. All spirits and strong wines should be given diluted. Alcohol is inappropriate after haemoptysis or in cases in which repeated haemoptysis is a feature. In gastritis, which often accompanies phthisis, alcohol is out of place. If cough is unusually distressing, good claret may be borne when other forms of stimulants produce irritation. The old idea of heroic doses seems to be retained only in connection with the last stages, when extreme debility and a tendency to fatal syncope may be counteracted by the use of spirits as a bracer, when necessary.

Loomis (quoted by Francine) is also a believer in alcohol used judiciously, and particularly in the later stages of the disease. He used it in small quantities with food or in the form of milk-punch in the forenoon or on retiring. He goes so far as to say that there are very few cases of

phthisis (advanced chronic febrile cases) which are not benefited at some period of their course by the discreet administration of alcoholic stimulants. He thinks that alcohol is one of those remedies which is capable of doing good, if judiciously used, while at the same time it is liable to do positive harm.

H. M. King (1906) stated that

> I am aware of being misunderstood in expressing an opinion indicating a middle course with regard to the use of alcohol in tuberculosis. Nevertheless, my experience leads me to hold such an opinion. If the patient is doing well, has a good appetite and digestion, and is gaining weight satisfactorily without alcohol, certainly there is no excuse for prescribing it. But, on the other hand, where there is a tendency to anorexia, where digestion is sluggish, especially where milk is ill borne, where weight gain is not satisfactory, and, of course, where there is no specific contraindication, I know of nothing else that will quite take the place of the light wines or malt liquors in promoting the building-up process for which we are striving. In such cases it is both a food, which is immediately available to the tissues, and a mild and harmless stimulant to digestion. It must be taken in moderation . . . . depending upon temperament, education and idiosyncrasy.

He prescribed light clarets, Rhine wines and even Burgundy at mid-day and evening meals, but did not forbid malt liquors. Distilled liquors, always well diluted, have a narrower field of usefulness. For the preceding fifteen years King has used alcohol in from 5 to 10 per cent of his patients, getting invaluable aid in some and no harm in any from its use. What has been said applies, he states, only to the use of alcohol in the dietetics of pulmonary tuberculosis.

A. P. Francine (1907) stated that

> Alcohol, for a long time a staple article in the diet of tuberculous patients, is now comparatively little used. The position of alcohol in the treatment of tuberculosis is in my opinion by no means settled except in so far as its general and indiscriminate use is concerned. In small amounts and in suitable cases, particularly old people, I believe it to be a reliable general tonic and a stimulant to the gastrointestinal function. In large amounts it has quite the contrary effect and if used at all must be used with wisdom. It may be prescribed in the form of beer, claret or porter once a day as outlined in the dietary above. Whisky, however, certainly has a place not yet fully understood in the treatment of these cases. We cannot ignore the empiricism which eventually led to its abuse. It would seem to be particularly indicated in those cases with dyspnoea and faulty circulation where a cardiac stimulant is called for. Be-

sides stimulating the gastric function it facilitates in a measure absorption of fats. In moderate doses (for it should be looked upon and used as a drug rather than as a food) it stimulates the nervous system and in selected cases a glass of beer or an egg nogg taken at night may favorably influence night sweats and sleeplessness. Though theoretically its effect on body temperature seems in doubt it has been used with favorable results in those cases where, following more or less prolonged and high pyrexia, the temperature becomes persistently subnormal. In such cases its stimulant and tonic effect facilitates the return of health and strength. It should never be used, as in former times, for any fancied specific action against tuberculosis. So far have the views changed on these questions that it is now considered a predisposing factor to the development of tuberculosis. Whisky should not be used continually but only where a definite indication exists for it and then as a therapeutic agent pure and simple. It should not be prescribed for children and care should be taken not to order its use where there is danger of creating the habit.

Bonney (1910) says that alcohol is rarely given as a cardiac or general stimulant save to people of advanced age. Used indiscriminately it adds to arterial excitement, increases the tendency to haemorrhage, impairs the appetite, and promotes restlessness and insomnia. When used in sufficient quantity to destroy the appetite and retard digestion the amount of food supplied by the alcohol is far less than the nutritive value of the food ordinarily taken. Its intelligent administration, however, in small doses and to carefully selected cases may be attended by considerable benefit. It is sometimes well to permit those with fickle appetite to take a mild dry cocktail 5 or 10 minutes before the mid-day or evening meal, but this should not be continued for any great length of time. It may add to the consumption of food. A light ale, stout or half-and-half, consumed with meals, is of some value as an appetizer and as an aid to nutrition. Taken during the evening it is frequently found to promote sleep. Occasionally a sherry, Rhine wine or Moselle may be served with the dinner. This constitutes the only manner of administration of alcohol which should be permitted, save in the presence of acute conditions demanding active stimulation.

Ritter (1923) says that in elderly individuals a teaspoonful of whisky or brandy, given in a little hot water and sweetened to taste, is often followed by a restful sleep.

Goldberg and Lorber in 1924, writing on the local effect of alcohol on experimental tuberculosis, conclude that ethyl alcohol in concentration of 30 per cent is not capable of producing profound local tissue changes and,

upon injection around a local intracutaneous site of infection with virulent human tubercle bacilli, has no appreciable effect on the development of the local tuberculous lesion, the local lymph-node involvement or the systemic disease. Likewise, compresses of 70 per cent alcohol (ethyl), applied locally to an intracutaneous site of infection with tubercle bacilli in guinea pigs, have no influence on tuberculosis developing subsequently. (Concentrations of ethyl alcohol, as low as 20 per cent in physiological saline solution, have a detrimental influence on virulent human tubercle bacilli when the bacilli are suspended therein for two hours at incubator temperature, while 10 per cent alcohol is without effect.)

Stillman (1924) discusses the persistence of inspired bacteria in the lungs of alcoholized mice. In the study a comparison was made of the time of disappearance of inspired pneumococci, haemolytic streptococci and *Bacillus influenzae* and the relative occurrence of generalized infection in the two groups of animals following inhalations of pneumococci. The animals were intoxicated by inhalations of alcoholic spray or by intraperitoneal injections of 1.5 cc. of 10 per cent alcohol in salt solution. The experiment threw no light on whether the inspired bacteria are killed *in situ*, are taken up by leucocytes, or are carried to other parts of the body; nor on how alcohol exerts its harmful effects, or whether alcoholic intoxication causes local changes in permeability of the respiratory mucosa or acts adversely on systemic resistance. They did show that alcohol delays the removal of inspired bacteria from the lungs and favors the invasion of the blood-stream. Stillman concluded that pneumococci which have reached lungs of normal mice as a result of this procedure usually disappear within a few hours, but in mice, which have been intoxicated by alcohol, pneumococci persist in the lungs for a longer period and fatal septicaemia frequently follows. He said, however, that the experiment yielded no evidence as to how alcoholic intoxication renders the lungs more permeable to inspired bacteria.

A brief survey of the American usage of alcohol in tuberculosis indicates that no one recommended it as strongly as did Flint. For years it has not been employed in the routine treatment of tuberculosis. All authors suggest carefully guarding against its abuse and few agree with Flint that alcoholism may not develop from its employment in the treatment. King's attitude toward alcohol developed from his treatment of well-to-do patients who long had been accustomed to its moderate use. It is highly probable that patients in the private division of his sanatorium were treated differently from those in the public divisions, where alcohol

was, most likely, sparingly used. The experimental evidence seems to us of slight value, but it is of interest to note that Stillman's work seems to bear out the opinion of Cornet that alcohol apparently lessens the expulsive force of the ciliated epithelium.

ALCOHOL IN THE TREATMENT OF TUBERCULOSIS

Alcohol is being used less and less in the treatment of tuberculosis. It was said that one of the greatest, if not the greatest, of all students in America of clinical pulmonary tuberculosis, Austin Flint of New York, dispatched some of his patients to the mountains with their trunks filled with bottles of whisky. At that time alcohol was considered a very efficient stimulant, not only by the patient, but also by physicians. Such a view is no longer held by physicians, and more recent pharmacological investigations suggest that after absorption alcohol acts rather as a depressant. It is of interest to note in passing that even in a country like France, where wine is consumed by a large proportion of the inhabitants, many articles have appeared on alcoholism and tuberculosis, calling attention to the importance of strong spirits (absinthe) as an aetiological factor in the production of the disease. Germany, too, has not escaped such articles, criticizing the use of alcohol in the treatment of tuberculosis and calling attention to its dangers as an aetiological factor in tuberculosis.

In the treatment of tuberculosis, particularly of the pulmonary form, the temperate use of alcohol has long been advocated, more particularly in the European institutions and health resorts, where intemperance in the use of such drinks occurs less frequently. It is of interst to note that even under such influences, with such surroundings, many Americans still fall into excesses. Some have called attention to the fact that many of the sanatoria abroad are conducted as private enterprises, and no doubt have a considerable income from the sale of wines and other alcoholic drinks. The physicians, who conduct such sanatoria, have always themselves been accustomed to the temperate use of such beverages, and naturally can see no reason why their patients should not indulge in what seems to them a harmless practice. The situation is very different in America, where for years it has been known that many who seek health either in open or closed health resorts, find that the time hangs heavy on their hands. In open health resorts in this country before the advent of prohibition it was always risky to permit a patient who "liked his liquor" to reside in a hotel with an open bar. Such patients were usually very

convivial and liked to drink in company. When a number of such boon companions foregathered on the hotel veranda, the majority drank much more than their treatment required. Not infrequently the only course to pursue in such cases was to send the patient to another health resort, and caution him and the physician to whom he was referred in regard to his weakness. Under prohibition this has been largely changed, but temptation in clubs and speakeasies is not unknown.

The justification of the use of alcohol in the treatment of tuberculosis depends, of course, upon the benefits derived from its value as a food, from its effect upon the disease itself or upon the latter's symptoms, or from its effect upon the general well-being of the patient. The direct effect of alcohol upon the tuberculosis is, in all probability, very slight, for no evidence has been adduced to show that following its use any more connective tissue is formed in the diseased area than in the usual case in which no alcohol is used. On the other hand, in susceptible and even in some robust individuals the prolonged overuse of alcohol may weaken the bodily resistance to the tubercle bacilli and to other germs. Those who have advocated alcohol have, however, based their claim for it largely upon its effect upon the symptoms of the disease. Turban noted that after the free use of alcohol the râles in the chest might be fewer, but this condition was only temporary.

As a food for use in pulmonary tuberculosis it cannot be recommended, for its value is slight, as the body can oxidize only about one or two ounces of pure alcohol in twenty-four hours, and this amount can easily be replaced by a little carbohydrate. It is recommended more frequently, however, in pulmonary tuberculosis as a tonic. When used in this manner, it should not flush the face but should increase the appetite. In some patients a cocktail or a weak highball containing a tablespoonful of whisky or cognac, taken just before or during the first part of a meal, may aid a capricious or flagging appetite, or indeed stimulate and aid a weak digestion. A glass of stout, of beer, of bitter ale, or of good wine may act in a similar manner. When the appetite is good, such a tonic is not necessary, though some affirm that the feeling of well-being that such moderate usage of alcohol brings about justifies its use. In patients, who require milk or eggs between meals and who cannot take them otherwise, a little sherry on the egg or a small amount of brandy or whisky in the milk is often recommended.

In some patients with insomnia a glass of beer or ale at bed-time or indeed a small drink of whisky may act as an efficient but possibly dan-

gerous remedy. Gin is at times taken for dysmenorrhoea, but for tuberculosis patients there are other more efficacious remedies. Late in the disease brandy and champagne are of great value in some cases, and a few patients with slowly progressing chronic disease unquestionably prolong their existence by a judicious, although rather free use of spirits.

The objections to the use of alcohol in pulmonary tuberculosis are numerous. Some maintain that more patients have been harmed than helped by its use. This is held to be true especially in cold and high climates. Alcohol should not be employed in cases in which it irritates the larynx, or increases or produces cough, or irritates the stomach or causes headache. It should not be given to patients following haemoptysis, nor for some time afterward. Many nervous, excitable patients are better off without it. In individuals long accustomed to it, usually of middle age, it should be rigidly limited, and, if such a temperate use of alcoholic beverages cannot be followed, it should be proscribed. In some patients, long accustomed to its use, its gradual withdrawal may be followed by excellent results. Alcohol, when taken in such quantities as to produce slight exhilaration, as to lessen in any degree the great caution necessary for successful treatment, as to facilitate the daily round of petty chores, becomes very dangerous. Except in small doses which are very often undeterminable for the individual patient, it is said to injure further the central nervous system, which in tuberculosis is at times already unhappily affected.

In the sanatorium treatment of pulmonary tuberculosis in this country alcohol is rarely prescribed. At the Trudeau Sanatorium it is practically never used. From time to time a few patients have been discharged for drinking; and drunkenness means immediate discharge. In many open health resorts, where patients, who have been accustomed to have wine and other alcoholic drinks at the table, seek health, the proscription of alcohol is not so absolute. After the advent of prohibition, for a number of years the writers did not apply for a license to prescribe liquor. More recently they have done so, and from December, 1928, to December, 1931, they have written 50 prescriptions for 28 patients with pulmonary tuberculosis, always at the request of the patients. In their opinion it is rarely necessary to prescribe any alcoholic drink in the treatment of tuberculosis of any form or type; and, when they have done so, it has practically without exception been for those who have been previously more or less accustomed to its use.

BIBLIOGRAPHY

ABADIE, J., AND GRENIER DE CARDENAL, H.: Les rapports sociaux de la tuberculose et de l'alcoolisme à Bordeaux, Congr. Internat. de la Tuberc., Paris, 1905.

ACHARD AND GAILLARD: Influence de l'alcool sur la marche de la tuberculose experimentale, Cong. Internat. de la Tuberc., 1905, Paris, 1906, i, 323.

ARNOULD, E.: Existe-t-il des concordances statistiques entre l'alcoolisme et la tuberculose? Rev. d'Hyg, 1925, xlvii, 614. (Abst. Zentralbl. f. Tuberk., 1925–26, xxv, 682.)

BANDEL, R.: Alkohol und Tuberkulosesterblichkeit, Zeitschr. f. Tuberk., 1929, lv, 238.

BANDELIER-ROEPKE: Clinical system of tuberculosis, 1913.

BERNARD, L.: La tuberculose pulmonaire. Alcoolisme et tuberculose, Par., 1921. (Abst. Zentralbl. f. Tuberk., 1922, xvii, 337.)

BONNEY, S. G.: Pulmonary tuberculosis and its complications, ed. 2, W. B. Saunders Co., 1910.

BRECHMANN, H. J.: Respirationsversuche nach Aufnahme von Alkohol sowohl wahrend der Ruhe als auch wahrend der Arbeit, Ztschr. f. Biol., 1927, lxxxvi, 447. (Abst. Zentralbl. f. Tuberk., 1928, xxix, 136.)

BREHMER: Cited by KINGHORN: The treatment of pulmonary tuberculosis by rest and exercise.

BURRELL: Recent advances in pulmonary tuberculosis, 1929.

CAPO, A. E.: Alcool et tuberculose, Congr. Internat. de la Tuberc., Paris, 1905.

CHEYSON, M.: L'alcoolisme, Ibid.

CONGREVE, G. T.: On consumption of the lungs or decline and its successful treatment, January, 1892.

ENGELEN: Alkoholgenuss bei Lungentuberkulose, Allg. med. Zentralzeit., 1921, xc, 109. (Abst. Zentralbl. f. Tuberk., 1922, xvi, 186.)

EWALD: Alkohol und Infektionskrankheiten. (Abst. Zentralbl. f. Tuberk., 1912–13, vii, 662.)

FOTHERGILL: Exercise and food for pulmonary invalids by Charles Denison, M. D., Denver, The Chain and Hardy Co.

FRANCINE, A. P.: Pulmonary tuberculosis. Its modern and specialized treatment, ed. 2, J. B. Lippincott Co., 1907.

GERWIENER, F.: Alkohol und Lungentuberkulose, München, Gmelin, 1922. (Abst. Zentralbl. f. Tuberk., 1922, xviii, 396.)

GOLDBERG, M. AND LORBER, M. B.: Local effect of alcohol on experimental tuberculosis, Amer. Rev. Tuberc., 1924, x, 454.

HALLOS-SZEGED, J.: Alkoholismus und Lungentuberkulose. (Abst. Zentralbl. f. Tuberk., 1912–13, vii, 208.)

HARRIS, V. D., AND BEALE, E. C.: The treatment of pulmonary consumption, P. Blakiston and Co., 1895.

HOLITSCHER: Alkoholismus und Tuberkulose, Beitr. z. Klin. d. Tuberk., 1913, xxix, 233.

JEX-BLAKE, A. J.: Tuberculosis. A general account of the disease; its forms, treatment and prevention, London, G. Bell & Sons, 1915.

KAMNEW-SCHUJA: Ist der Alkohol fur dem Phthisiker schädlich oder nutzlich? (Abst. Zentralbl. f. Tuberk., 1913–14, viii, 277.)

KLEBS, A.: Tuberculosis, D. Appleton & Co., 1909.

KNOPF, S. A. Pulmonary tuberculosis. Its modern prophylaxis and the treatment in institutions and at home, P. Blakiston & Co., 1899.

KOLBER, A.: Tuberculose et alcoolisme, Internat. Ztschr. gegen d. Alkoholismus, 1925, xxxiii, 337. (Abst. Zentralbl. f. Tuberk., 1925–26, xxv, 682.)

LATHAM, A.: The diagnosis and modern treatment of pulmonary consumption with special reference to the early recognition, London, Balliere, Tindall & Cox, 1905.

LILIENTHAL: J. Orth's Vortrag, Ztschr. f. Tuberk., 1915, xxiii, no. 4.

MOUISSET, F.: Alcoolisme et tuberculose, Jour. de Méd. de Lyon, 1922, iii, 125. (Abst. Zentralbl. f. Tuberk., 1922, xviii, 396.)

ORTH: Alkohol und Tuberkulose. (Abst. Zentralbl. f. Tuberk., 1915, ix, 560.)

OSLER, W.: American System of Pratical Medicine. LOOMIS-THOMAS: Article on Tuberculosis.

PREBLE, E. On the use of alcohol in phthisis, Jour. Tuberc., 1901, iii, 316.

RITTER, J.: Handbook of tuberculosis for medical students and practitioners of medicine, Chicago, 1923.

SAMSON, I. W.: Alkoholismus und Tuberkulose, Deutsche med. Wchnschr., 1924, l, 613.

SCHEMITZ, R.: Tuberolosi ed alcoolismo. (Abst. Zentralbl. f. Tuberk., 1929, xxx, 869.)

SEIFFERT: Alkohol und Tuberkulose. Alkoholfrage, 1922, xviii, 94–99; 121–128. (Abst. Zentralbl. f. Tuberk., 1922, xviii, 519.)

SQUIRE, J. E.: The hygienic prevention of consumption, London, Chas. Griffin & Co., Exeter St., Strand, 1893.

STILLMAN, E. G.: Persistence of inspired bacteria in the lungs of alcoholized mice, J. Exper. Med., 1924, x, 454.

WALTERS, F. R.: The open air or sanatorium treatment of pulmonary tuberculosis, London, Balliere, Tindall & Cox, 1909.

WALTERS, F. R.: Sanatoria for consumptives (a critical and detailed description together with an exposition of the open air or hygienic treatment of phthisis), New York, E. P. Dutton & Co.

CHANGE OF CLIMATE AND ALTITUDE

I. ITS EFFECTS ON TUBERCULOSIS PATIENTS

E. W. PHILLIPS[1]

INTRODUCTION

For the past ten years St. Luke's Home, a sanatorium located at Phoenix, Arizona, has maintained two institutions for the care of one group of tuberculosis patients. On or about the first of June each year the Phoenix plant is closed, and those patients considered suitable for the move are transferred to the summer sanatorium at Prescott, Arizona, where they remain until the first of October, returning then to Phoenix. This means a considerable change of both climate and altitude. Phoenix is 1,079 feet above sea-level; it lies in an irrigated valley surrounded by desert. Prescott has an altitude of 5,300 feet, and is situated in a mountainous country where there are running streams and large pine forests. The patients are subjected to no change other than that of environment. They have the same medical and nursing care, even the same cooks, and the buildings are equally comfortable. If there is a demonstrable difference between mountain and desert climates, between high and low altitudes, in their effect on the course of pulmonary tuberculosis, it should be apparent in the record of these patients.

This paper is based on the records of 309 patients observed for an average time of eleven months each during the five-year period ending with December, 1930. Its first part attempts to show the effect of altitude and climatic change on body-weight, pulse, temperature, and the tendency to haemorrhage. The second part will record certain variations in treatment made necessary by the changed altitude; it will describe the few cases in which the reaction to the higher altitude was unfavorable, and will offer evidence that for most consumptives such a biennial change under controlled conditions is beneficial.

The clinical material observed was made up of 192 men and 117 women, all white and nearly all Americans.[2] The women were the younger; only

[1] Phoenix, Arizona.

[2] Eleven of these patients had acquired their disease in Arizona. The others came from all parts of the United States, with a few from Canada.

three were past fifty, and 75 per cent of them were between the ages of 20 and 35, while only 59 per cent of the men came within this age-group. Most of both sexes had been low-salaried workers of one sort or another. As to their physical condition, two-thirds of these patients (67.6 per cent, to be exact) were classified as far advanced. By local standards this means a selectively admitted group. In earlier years only those patients whose course was favorable and whose general condition was good had been taken to the mountains. Experience showed that so much caution was not required, and the patients whose records are here reviewed were the regular sanatorium population with two classes excluded, —the known hyperthyroid, and those whose apnoeic pause (the non-breathing time possible to the individual at the end of an ordinary expiration) was less than 12 seconds, with 15 seconds as a preferable minimum. These indications of intolerance to high altitude will be discussed later.

The five-hour trip from one sanatorium to the other is made in a special chair-car. No damage has ever resulted from the journey, and it can be disregarded in estimating the effect of change of altitude.

The seasonal cycle in which these patients lived is marked by reduplications. They experience a mild winter in the Valley, with considerable frost, a little rain, and no snow. This is followed by a dry spring season, which goes on to what would be called in most parts of the country a hot dry summer. Then on June first they go to the mountains and are again in a spring climate. The mountain summer is brief, and in July and August it is marked by electrical storms. There is light frost before the first of October, when the patients return to the Valley and are once more in late summer. This climate with its seasonal changes is shown graphically in chart 1 (1) (2). The percentage of possible sunshine is high at all seasons. The relative humidity is low, and, what is important for comfort, it is lowest when the temperature is highest. Its curve, however, is the reverse of the curve of possible sunshine and not of that of the mean temperature, as would happen in a coastal region. The mean temperature ranges from 52°F. in midwinter to 80°F. at the end of May, but the diurnal range is nearly 30°F., so that the climate is essentially stimulating rather than uniform.

BODY-WEIGHT

An entirely objective phenomenon, the change in body-weight, was studied first. In computing data for the curves, the weights on the last

weighing day of each month, and the mean monthly temperatures, were used. This method was employed not only in the interest of simplicity; it appears to present a more nearly accurate picture of the conditions

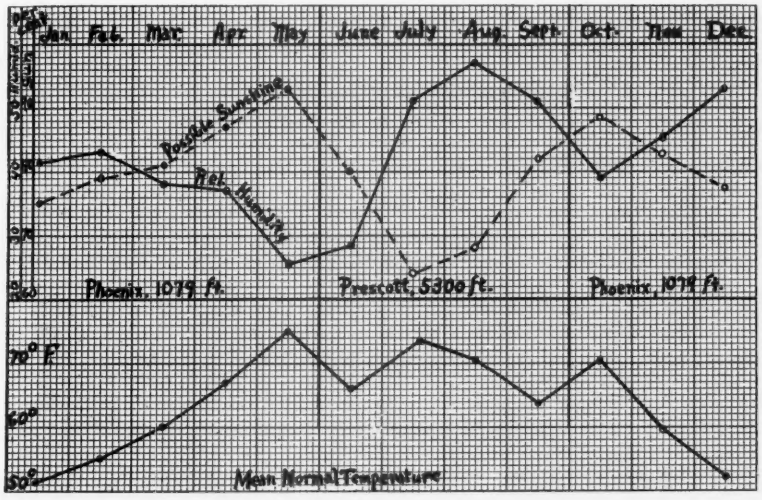


CHART 1. SHOWING CLIMATIC ENVIRONMENT OF TUBERCULOUS PATIENTS MOVED FROM LOW TO HIGH ALTITUDE DURING SUMMER

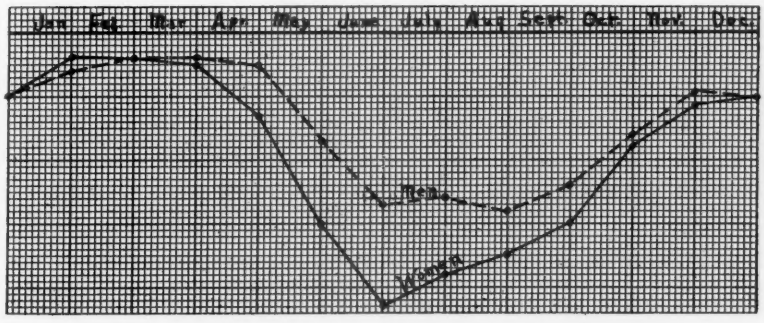


CHART 3. SEASONAL WEIGHT CHANGE OF MEN AND WOMEN, CORRECTED FOR ANNUAL GAIN

The curves are not related to any element of the climate shown in chart 1.

present from year to year. As an experiment, the weekly weights during one spring and summer were plotted along with the climatic data. Except for irregularities caused by accidental or nonrecurring factors, the curves much resembled those of the five-year period. It did not appear

that brief variations in either the mean or the maximum temperature of the air had any constant effect on the seasonal trend of the body-weight curve.

It happens that in this institution one-third of the year's admissions occur in the first three months of the year. Since a newly admitted patient usually gains weight for a few weeks, whatever his subsequent course may be, this fact is to be remembered in interpreting the graphs of actual weight change shown in chart 2. The error from this source can hardly exceed 4 per cent in favor of the spring months. If admissions were

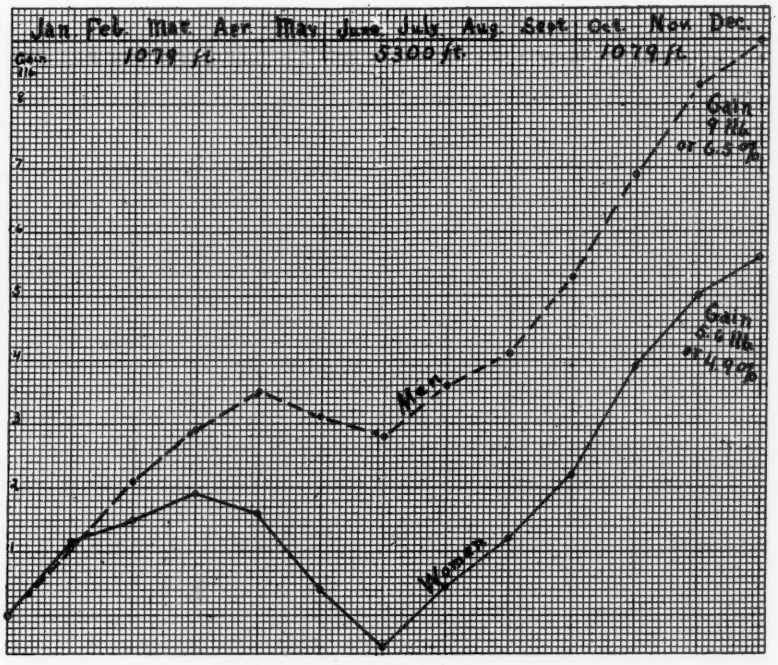


CHART 2. ACTUAL SEASONAL WEIGHT CHANGE OF MEN AND WOMEN

Average admission weight of men, 137½ lbs.; of women, 115 lbs.

uniformly distributed throughout the year, the graphs would still show that the average patient increases in weight during nine or ten months out of the twelve, that the rate of increase is definitely related to the seasons, and that the sexes differ in this respect.

Eighty-two per cent of the men gained weight. Entering with an average weight of 137½ pounds, they made a moderate steady gain from January until the last of April. In May and June they lost a little; in

July and August they gained, but slowly; then they increased in weight more rapidly as the days grew shorter, and came nearly to a standstill at the time of the winter solstice. In a year their average gain was 9 pounds, or 6.5 per cent of their admission weight.

The women gained proportionately less than the men, and they exhibited a greater sensitiveness to seasonal influences in their weight increase. Only 73 per cent of the women gained weight during their stay in the sanatorium; the others remained stationary or lost. Entering with an average weight of 115 pounds, the women gained slowly during the first three months of the year. In April they lost a little; in May and June their weight fell off, until at the end of June it averaged below their admission weight. From July to the end of the year they gained steadily, their net increase being 5.6 pounds, or 4.9 per cent of their admission weight.

This lesser tendency of tuberculous women to gain weight, while it varied somewhat from year to year, was present in each of the five years covered by this observation. It was likewise noted in the group of patients, not here discussed, who were treated during the Phoenix season but who did not go to the mountains. What is the reason for such a disparity? Is it because women are readier than men to seek medical relief, less burdened with responsibility, and so come under treatment while still near their normal weight? This is true, of course, but it applies with minimal force to the women of this group, most of whom were self-supporting. Nor were the women worse damaged by disease than were the men; on the contrary, only 62 per cent of the women were classed as far advanced, as against 71 per cent of the men. And, as has been said, the women were the younger. There must be some intrinsic reason why their seasonal loss of weight exceeds that sustained by a comparable group of tuberculous men living under exactly the same conditions, and such a reason can be found only in the behavior of their endocrine glands. As has been stated, practically all of these women were below the age of fifty. The recurring menstrual cycle, often preceded by ten days of slight fever, the greater liability of women to the anaemias, and the relative instability of their thyroid function, are all to be taken into account in explaining the phenomenon.

This loss of weight in early summer, observed in tuberculous women and to a lesser degree in a comparable group of men, is not a function of altitude, for it was well under way before the patients left the Valley. It was not caused by hot weather, for the loss continued unchecked after

transfer to the cool of the mountains in June. It did occur at a time when the air was excessively dry, but this relation is probably only apparent, for loss of weight continued for a month in the new environment with a rising relative humidity.

Simple loss of body fluids cannot explain the phenomenon. Long before the beginning of this series, the sanatorium routine had been adjusted to take care of the matter of water-balance. Patients are taught that water, taken especially in the morning and between meals, is as important as food in gaining and holding weight. In hot weather they are not permitted to fill up with iced drinks at meals, to the detriment of their appetites; so they resort the more to the thermos jugs which are part of their bed-side furniture. Also, they wear the scantiest of clothing during the heat of the day, taking air-baths in bed during the afternoon rest. Those who took sun-baths discontinue them in May. That these measures compensated for the considerable loss of water which is bound to occur in hot dry air, is shown by the fact that patients newly admitted in early summer made their initial weight gain as well then as at any other season. But the loss of the group occurred each year in spite of attention to water-balance, attractive summer food, and all other efforts to prevent it. This loss bears no constant relation to heat, sunshine or humidity, and there is nothing to show that transfer from a low to a high altitude accentuated the seasonal decline in body-weight. More reasonably, it may be argued that the bodily comfort of the cool summer held this seasonal decline to a minimum, both in extent and in duration.

This point becomes clearer if one-twelfth of the annual gain be subtracted from the actual weight at the end of each month. The result, which approximates a normal seasonal weight graph of the two groups studied, is shown in chart 3. When corrected for the annual gain, the weight curves of the two sexes become nearly parallel. Both are deformed upward in February and March because of the initial gain made by the greater number of patients who enter in late winter. Both men and women experience a relative loss of weight from the first of April to the first of July, but the women lose more. From July to December they gain in weight, but come to a standstill in midwinter.

These figures much resemble the weight-curves of tuberculous patients in England, or India, or Denmark, or wherever in the northern hemisphere such data have been recorded. But the components of the climate here are quite different, and the theories as to the influence of the various climatic factors on body-weight, sponsored by other observers,

are not confirmed by this study. For example, Lunde's Norwegian patients made a marked gain in late summer and in autumn (3), when air-temperature was moderate (for Norway) and a high relative humidity favored the retention of water within the body; these Arizona patients also gained at the same time of year when the temperature was rather high and the relative humidity, always lower than that of Norway, was falling. And at the same season Pai's (4) patients at Madras made a similar gain while both temperature and humidity were high.

Nor does the direction of the temperature-curve, the continued trend from cooler to warmer, or the reverse, explain the change in body-weight. These Arizona patients lost weight in May in a mean temperature of 75°F.; they continued to lose weight in June, though the mean temperature was nine degrees lower. They gained in the mountains in September when frost was on the ground; they continued to gain in Phoenix in October when they slept on porches with one blanket for cover; and, as the winter solstice approached, their weight became stabilized for a time, as it does elsewhere.

The weight-curves of these patients are not clearly related to the altitude in which they lived at the time, nor to any element or combination of elements in the climate. While the cool mountain summer added to the patients' comfort of mind and body, it did not demonstrably affect their weight. Their seasonal variation in body-weight seems to be governed by endocrine factors; it is related inversely to the length of the days and to the intensity of solar radiation; apparently it is analogous to the biological phenomenon which finds its clearest expression in the hibernating animals.

PULSE-RATE

When a person accustomed to living in low altitudes first goes to the mountains he experiences certain effects, some pleasant, others rather disagreeable. He feels stimulated, even to the point of wakefulness at night, and his appetite is increased; but on exertion he is conscious of shortness of breath and of a rapid forcible heart-beat. This is a normal phenomenon. At a moderately high altitude, such as is here considered, the body soon adjusts to the changed conditions and one gets, as the saying is, his "mountain wind." This adjustment becomes easier the oftener it is made, but only those who were born and raised in the mountains do not feel the altitude after a winter in the Valley.

To prevent possible damage during this period of adjustment, the

exertions of the group of patients whose records are here studied were kept to the minimum. For the first ten days in the mountains exercise and sun-bathing were forbidden, and stricter bed-rest was enforced. After this period they gradually resumed the routine of treatment to which they had been accustomed in Phoenix. By reason of this precaution, the initial effect of altitude change is not shown in their graphic pulse-records, which are fairly constant for each individual during the months spent in the higher altitude. A considerable number of these records, however, do show a definite altitude effect on the pulse.

Nine cases were discarded because some extraneous factor, such as the development of hyperthyroidism or the administration of digitalis, influenced the heart-rate; the records of 186 men and 114 women were suitable for this study. It was at once apparent that tuberculous patients of the two sexes reacted alike to altitude change so far as their pulse-rates were concerned. Thus, 43 women, or 37.7 per cent of the women, had a pulse-rate higher in the mountains; 70 men, or 37.6 per cent of the men, showed a similar increase in pulse-rate; and for each sex the average increase was 7 beats per minute. The percentages in the other groups were also very close together.

According to the effect of altitude on their pulse rates, the 300 patients fell naturally into five groups. One hundred and thirteen, or nearly 38 per cent of the total, had a pulse-rate seven beats per minute higher in the mountains. This acceleration had no apparent relation to the course of their disease, for 82 per cent of them ran a favorable course while under treatment. Seventy-six, or 25 per cent of the total, had the same pulse-rate in the higher as in the lower altitude, and the same proportion of these, 82 per cent, were recorded as favorable. Fifty, or 16.6 per cent of the group, actually had a lower pulse-rate in the mountains. Whatever its cause, this unusual behavior was not of good prognostic import, for only 60 per cent of this group improved while in the institution.

Besides these, there were 54 patients whose pulse-rates steadily declined, no matter in which altitude they happened to be. These were all patients admitted with active disease and lively constitutional symptoms, who responded well to treatment. All made satisfactory progress, with the exception of one who developed tuberculosis of the colon. Another group of seven did just the opposite: their pulses became faster in any altitude, and all seven steadily grew worse. They had, of course, active disease which progressed in spite of treatment.

Table 1 shows the situation at a glance. It may be summarized by

saying that more than a third of these tuberculosis patients, when moved from a low to a high altitude, experienced a moderate acceleration of the pulse-rate during their four months' stay in the mountains. This higher rate was not associated with any increased activity of their disease; it had no unfavorable prognostic significance. One-fourth of the group did not respond to the higher altitude by any change in pulse-rate. One-sixth of the total number had a slower pulse-rate in the mountains, and this was not a favorable sign. The significant finding here is that patients with advanced tuberculosis can safely be moved to an altitude of 5,000 feet, provided the proper precautions are observed; the moderate increase in the pulse-rate which occurs in one out of three such cases is not to be interpreted as an adverse omen.

TABLE 1

Effect of altitude on pulse-rate

PULSE-RATE	NUMBER OF PATIENTS	PER CENT OF TOTAL	PER CENT FAVORABLE
Higher in mountains	113	38	82
Same, both altitudes	76	25	82
Lower in mountains	50	17	60
Steady decline	54	18	98
Steady increase	7	2	0
	300	100	

BODY-TEMPERATURE

The ability of the human body, whether sound or diseased, to maintain a stable temperature under varying atmospheric conditions was illustrated in the records of this group of tuberculous patients. As shown in chart 1, the temperature and humidity of the air varied considerably, but not beyond the elastic limits of the heat-regulating mechanism. The only exception is found in the records of the first hot days of May of each year, when, with an atmospheric temperature above 100°F. and a low relative humidity, some 20 per cent of the patients showed body temperatures from one-half to one degree higher than they usually had. This elevation was transient; the same atmospheric conditions later in the month were not similarly reflected on the temperature-charts.

Though pulse and temperature are usually charted on the same sheet and considered together in estimating the degree of activity present in

pulmonary tuberculosis, their curves were not parallel nor their meanings identical in this series of chronic and mostly far-advanced cases. The advent or increase of fever was regularly accompanied by an increase of the pulse-rate, but the converse was not true. As has been related, more than one-third of the patients had faster pulses in the higher altitude with no related increase in other clinical signs. Fever, on the other hand, seemed to be governed entirely by absorption from disease foci. Excepting again the few hyperthyroid cases reserved for later discussion, the body-temperatures of the group of tuberculous individuals under consideration were not affected by change of climate or change of altitude in either direction. They continued in one place the trend, whether normal or febrile, which had been established in the other location, and any marked and sustained change in the temperature-curve was accompanied by a change in the disease picture to account for it. Thus, 172 patients had normal temperatures unchanged by transfer. Fifty-eight had higher average temperatures in the mountains, but most of them were admitted there with active tuberculosis. Similarly, 79 patients had more fever in the Valley, and all but eight of them were admitted there. In either case, the higher temperature at the place of admission was incident to active disease which was subsiding when it came time to move; the few exceptions were instances of progressive disease which persisted in either altitude.

In this study of a group of the chronic tuberculous, nothing was found to show that change of climate and altitude demonstrably affected the body-temperature.

HAEMORRHAGE

When a group of tuberculous persons, three-fourths of whom have open cavities, reside in any place for eleven months, it is to be expected that a considerable number of them will exhibit the phenomenon of haemoptysis. In this group of 309 such patients, 52, or nearly 17 per cent, bled from the lungs while in the institution. It remains to be shown whether change of altitude affected the frequency or the severity of the haemorrhages.

Twenty-seven had haemorrhages only in Phoenix; seventeen bled only in Prescott; eight bled while in both low and high altitudes. These 52 haemorrhage patients spent in the aggregate 391 months in the Valley, altitude 1,079 feet, and while there they had 78 haemorrhages, or on the average one haemorrhage every 5 months. They resided a total

of 196 months in the mountains, altitude 5,300 feet, and there had 40 haemorrhages, one to each period of 4.9 months, an incidence which is practically the same as in the Valley. Five of the 78 haemorrhages in the low altitude resulted fatally; two of the 40 haemorrhages in the mountains, where the time spent was half of that spent in the Valley, ended in death.

It will be recalled that these patients, when first taken to the mountains, were kept unusually quiet for ten days. Given this reasonable protection, the patients of this series showed no more tendency to haemorrhage in an altitude of 5,300 feet than they had at 1,079 feet above sea-level, and the danger of fatal haemorrhage was not increased by residence in the mountains.

SUMMARY

Three hundred and nine patients with pulmonary tuberculosis, who resided during the winter in a sanatorium situated near Phoenix, Arizona, at an altitude of 1,079 feet, were moved during the summer months to a sanatorium in the mountains at an altitude of 5,300 feet, returning to Phoenix in October. Their records are reviewed to determine the effect of such climatic change. In this paper the effect on body-weight, pulse, temperature, and the tendency to haemorrhage is discussed.

Two-thirds of the patients were classed as far advanced. Only the known hyperthyroid and those whose apnoeic pause was markedly shortened were denied treatment in the higher altitude.

The seasonal cycle in which these patients lived was marked by reduplications of early summer and late summer, with dry air, abundant sunshine, and comfortable outdoor temperatures throughout the year.

The body-weight curves of these patients showed a definite seasonal trend, apparently related to the length of the days and the intensity of solar radiation. They lost weight from April to July, and gained during the other months. Body-weight in this group was not governed by air temperature, relative humidity, or percentage of possible sunshine, nor was it affected by change of altitude in either direction.

Women gained proportionately less weight than men, and exhibited a wider seasonal variation in their weight.

More than one-third of men and women alike, when moved from a low to a high altitude, showed a moderate acceleration of the pulse-rate. This faster pulse was not accompanied by any increase in the clinical

activity of their disease; it had no unfavorable prognostic import; it subsided on their return to the lower altitude.

The body-temperatures of these patients, whether febrile or normal, were not affected by change of climate and altitude.

The incidence of pulmonary haemorrhage was almost exactly the same in the higher altitude as in the lower. Tendency to haemoptysis was not found to contraindicate transfer to the mountains, though all patients so transferred were kept unusually quiet during the period of adjustment.

Discussion of unsuitable cases, and presentation of evidence that most consumptives were benefited by the biennial climatic change, is reserved for later publication.

REFERENCES

(1) Data for Phoenix furnished by U. S. Dept. of Agriculture, Weather Bureau Station, Phoenix, Arizona.

(2) Data for Prescott furnished by Milton Updegraff, B.C.E., B.S., M.S., formerly official observer at Prescott, Arizona.

(3) Lunde, N.: The effect of the seasons on the general condition and increase in weight of the tuberculous patient, Tubercle, 1925, vi, 323.

(4) Pai, M. K.: On seasonal variations in body weight in pulmonary tuberculosis, Ibid., 1929, x, 212.

A COMPARISON OF CERTAIN MEDIA FOR THE CULTIVATION OF TUBERCLE BACILLI FROM SPUTUM[1]

M. F. SHAFFER

While a large number of media of varied composition has been proposed for the cultivation of tubercle bacilli from infectious material such as sputum, most of the media which have found widespread use for this purpose utilize as the basic ingredient either potato or egg or both. Each is definitely known to be useful, but their relative values have not yet been satisfactorily determined, so that the use of one or the other is still a matter of personal experience and preference. Meller (1927) claims that on egg medium the growth is more profuse and more rapid, while on glycerin-potato it is more certain. Schrader (1927) recommends the use of both glycerin-potato and egg tubes for diagnostic purposes.

The glycerin-potato cylinder of Pawlowsky (1888) has been used at some time by nearly all investigators. On the modification of Corper and Uyei (1929) contaminating overgrowths are often inhibited by the crystal-violet solution in which the slants have been soaked before tubing, while the development of the tubercle bacillus is not retarded. These workers reported their pre-treatment and medium to be superior to those of Petroff, equal to guinea-pig inoculation and more delicate than microscopic examination, particularly when the number of tubercle bacilli per cubic centimetre is small. Malkani (1929) likewise found that the Corper-Uyei method and medium yield a larger number of positive results than do those of Petroff.

Of the egg media, one of the first and simplest is that of Dorset (1902); this has been used throughout the world, the work of Brown and Smith (1910) having demonstrated its value for cultures following antiformin treatment. Burn (1922) found over a period of years that the only medium with which it was possible to obtain primary cultures consistently was the medium of Dorset or one of its modifications.

Closely related to Dorset's medium and differing only in the addition of glycerinated nutrient broth is the medium of Lubenau (1907). This or

[1] From the Sir William Dunn School of Pathology, Oxford University, Oxford, England.

its modification by Hohn (1926) has been employed with considerable success by Jacobi (1927), Matthies (1928), Hauptmann and Burtscher (1928), Sonnenschein (1927) and numerous others.

Petroff's (1915) gentian-violet meat-egg medium and sodium-hydroxide treatment have been as widely used as any. A host of workers, including Keilty (1915), Stewart (1917), Limousin (1921), Despeignes (1922), Moreau (1922), Tzetzu (1922), have found Petroff's method to be of value in the isolation of tubercle bacilli from a variety of sources. A number of slight changes in the original formula have been suggested. Corper, Fiala and Kallen (1918) added beef-extract plus peptone instead of veal infusion to the eggs in Petroff's medium; inspissation as a method of sterilization seemed to have no advantage over a single careful autoclaving. Sanchez (1924) advises that the concentration of gentian-violet be kept as low as possible; crystal- or methyl-violet may be used as substitutes. He obtained results comparable to those with Petroff's medium by simply impregnating the surface of Dorset's slants with a few drops of dye solution.

The medium of Sweany and Evanoff (1928), which contains, in addition to eggs, veal infusion prepared with sterile milk containing 15 per cent glycerin, has been hailed by its authors as being unusually well adapted for the cultivation of human tubercle bacilli; on it sediments may be inoculated directly without preliminary treatment involving the use of harmful agents. Dscheng Li (1930), however, has found this medium to be inferior to the media of Lubenau and Petragnani, particularly in the case of contaminated material pre-treated with sulphuric acid.

Petragnani's medium (1926) has been highly recommended by nearly all who have worked with it. Lichtenstein (1928) compared the media of Dorset, Lubenau, Petragnani, Hohn, and Loeffler's serum; Petragnani's medium proved superior to the others. Blumenberg (1929) and Blechmann (1927) found it more favorable than Petroff's medium in rapidity and total numbers of positive results, while Dscheng Li concluded that it was practically the equal of the Lubenau-Hohn medium when the malachite-green was omitted. On the other hand Frongia (1927) noted only sparse development of the organism on Petragnani's medium in the absence of malachite-green, while the addition of 0.05–0.3 per cent of the dye resulted in excellent growth. Wolters and Dehmel (1930) not only obtained good cultures, but were able with the aid of this medium to differentiate between human and bovine strains.

In view of the claims which have been advanced in favor of one me-

dium or another and the varying reports in the literature, it seemed desirable to carry out a comparative study to determine their relative value for the primary cultivation of tubercle bacilli from sputum. A number of specimens (42) were therefore obtained, treated to destroy contaminants, centrifugated, and the sediments inoculated on to the surface of slants of the various media. For pre-treatment the sulphuric-acid method of Corper and Uyei (1927) was used with slight modification, as previous work had shown it to be extremely efficacious.

METHOD

In this series the specimens were treated within six hours after collection in sterile stoppered bottles. When brought to the laboratory the bottles are thoroughly shaken to mix the material as evenly as possible. Then approximately 1 cc. of sputum is poured into a sterile 15-cc. graduated centrifuge tube, the volume determined, and an equal volume of 6 per cent sulphuric-acid solution (17 cc. of sulphuric acid, specific gravity 1.84, in 500 cc. of solution) added. The contents are mixed with a sterile glass rod until it contains few if any large particles. Of this mixture 2 cc. are now transferred to a second 15-cc. sterile centrifuge tube, with care to pour the fluid directly into the bottom, so that it does not flow along the side of the tube. The above procedure has two advantages. Frequently the sputum is so mucopurulent and tenacious, even after shaking, that it is very difficult to measure it into the first centrifuge tube in anything like exact quantities, but when it has been homogenized with an equal volume of acid it flows much more easily and may readily be poured into the second tube, permitting more accurate measurement. Furthermore, if it has flowed along the side of the first tube there may be some sputum which does not mix with the acid, so that the contaminants which are all too frequently present are not killed. If after thorough mixing the sputum-acid mixture is poured carefully into the second tube, so that none is left on the side, the danger of subsequent contamination of the media from this source is almost entirely eliminated. In the first 6 specimens of this series for which the precaution was not observed, contamination of the culture tubes was a serious difficulty.

After incubation in the dark for 30 minutes at 37°C. the tube containing the 2-cc. mixture is removed, 10 cc. of physiological saline solution is added, the whole stoppered, shaken vigorously and centrifugated at 3,000 r.p.m. for 6 to 10 minutes. The supernatant fluid is then poured

off and the sediment resuspended in a second 10 cc. of physiological saline. The tube is again thoroughly shaken, allowed to stand for five minutes, once more shaken, and centrifugated for 10 minutes at 3,000 r.p.m. After pouring off the supernatant fluid the sediment is used for the inoculation of the culture tubes. The two dilutions with saline serve to reduce the strength of acid to concentrations which are not measurably harmful to growth even when added to the medium.

In inoculating the media, the sediment is stirred with a few drops of saline to render it fluid. Then several drops may be allowed to flow slowly from a pipette over the slanted surface of the medium; or a number of loopfuls may be carefully streaked with the aid of a platinum or nichrome loop. The tubes are plugged with cotton dipped in paraffin-vaseline mixture to prevent drying, capped with tinfoil and placed in the dark at 37°C. They are observed from time to time for signs of growth, using a hand lens when necessary.

Sputum smears are prepared from material in the original collection bottles, as well as from the treated sediment, a portion of which has been used for inoculation. After staining by the Ziehl-Neelsen method the slides are carefully searched for acid-fast bacilli; if the organisms are rare, the slides are searched for 10 minutes or longer. Each negative or doubtful smear is checked by another experienced worker.

One tube of each of the media described below was inoculated with sediment from each specimen. For the 42 sputa examined, the total number of tubes prepared was 252.

The sputa were obtained from patients at the Cambridge Tuberculosis Hospital, Cambridge, Massachusetts. While they were taken from patients undergoing treatment for pulmonary infection, it will be seen from the results given below that not all of them were positive for tubercle bacilli with either method.

PREPARATION OF MEDIA

Medium of Corper and Uyei

Potato cylinders are prepared with the aid of a cork-borer, using well-scrubbed large potatoes. The cylinders should have a diameter of 0.5 inch and a length of about 3 inches. These are next cut obliquely to form slants with a short butt and large surface for inoculation. The peel at the ends of the slants having been removed, the slants after washing in tap-water are soaked for two hours in a 1 per cent sodium-carbonate solu-

tion containing 0.001,5 per cent crystal-violet. They are then wiped dry and placed in test-tubes, small glass rods which support the slant and sufficient 5 per cent glycerin-nutrient broth to immerse the butts having been previously added. After autoclaving for 20 minutes at 15 pounds pressure, the medium is ready for use.

Dorset's Medium

The contents of fresh eggs whose shells have been sterilized are placed in a sterile beaker. Add water to the extent of 10 per cent of the weight of the eggs, mix, and to the mixture add 3 per cent by weight of glycerin. Stir the whole carefully to avoid the formation of bubbles; filter through sterile gauze, tube, and coagulate the medium in the form of slants by heating in the inspissator or thermostatic oven at 90°C. for 1½ hours. To each tube add 5 drops of sterile 5 per cent glycerin-nutrient broth; inspissate at 80°C. for one hour on two successive days. Test for sterility by incubation at 37°C. for 3 days in a dark moist chamber.

Lubenau's Medium

The contents of fresh eggs are mixed with 5 per cent glycerin-nutrient broth in the proportion of 10 eggs to 200 cc. of broth. After filtration through sterile gauze the medium is treated in the same way as Dorset's medium.

Petragnani's Medium

Mix together in a beaker 300 cc. of fresh milk, 2 gm. peptone, 12 gm. potato meal and two finely grated potatoes each the size of a hen's egg. Place the beaker in a boiling water-bath, stirring the mixture constantly for ten minutes. Then allow the beaker to remain in the water-bath for an hour; at the end of this period it is removed to permit the mixture to cool to 60°C. Now add 8 whole eggs, 2 egg-yolks, 24 cc. of glycerin, and 20 cc. of a 2 per cent aqueous solution of malachite-green. Stir well to obtain thorough mixing, filter through gauze, and tube. Slant and coagulate the medium at 90°C. for 1½ hours; sterilize by inspissation at 80°C. for 20 minutes on two successive days. Test for sterility in the usual manner.

Petroff's Medium

A pound of finely ground veal is infused over night with 500 cc. of 15 per cent glycerin solution, the whole being kept in the ice-box with

TABLE 1

Period of incubation, six weeks

SPECIMEN NUMBER	MICROSCOPIC FINDING	CORPER-UYEI	DORSET	LUBENAU	PETRAGNANI	PETROFF	SWEANY-EVANOFF
1	+	c	c	c	(c) +	(c) +	c
2	+	++++	c	c	c	c	c
3	+	+++	c	c	+++	c	c
4	+	++++	+++	c	c	+	
5	+	++++	+		++++		++++
6	+	c	+++	c			c
7	−	+	++		++		
8	+	++++	+++		c	++++	
9	+	++	+				
10	+	++++	+++		++++	++	
11	+	++			++		
12	−						
13	+	++++			++++		
14	−	++++	+++		++++	+++	++++
15	+	+++	+++		++++	+++	++++
16	−						
17	+	+++		++	++++		++
18	+	++++				++	++++
19	−			++++	++++		
20	+	++++	+	++++	++		++++
21	+	++	+++	++++	++++		+++
22	+	++		+	+		
23	+	+++	+	+	+		
24	−						
25	+						
26	?	+++		++++	++++		
27	+	+					
28	+	++++		+++	++++		
29	+	++		+			
30	+						
31	−				+++		c
32	+	++++	+++	++++	+++	++	
33	+	+++	++	++++	+++		++
34	+	++++	++++	+++	++++	++	+++
35	+	+++		++	+	+	++++

TABLE 1—*Concluded*

SPECIMEN NUMBER	MICROSCOPIC FINDING	CORPER-UYEI	DORSET	LUBENAU	PETRAGNANI	PETROFF	SWEANY-EVANOFF
36	+	++++		++	+	+	++++
37	?	+++		+	++++		+
38	+	++++			+		+
39	+	++++		+++	c	+	c
40	+	+++		+++	++++	+	
41	+	++++		++			
42	+	++++					
Positive.....	33	33	15	18	27	13	13
Negative....	7	9	27	24	15	29	29
Doubtful....	2						

Total positives detected using microscopic examination: 33.
Total positives detected by the use of culture tubes: 37.

Microscopic results

+ = acid-fast bacilli present.
− = acid-fast bacilli absent.
? = presence of acid-fasts doubtful.

Culture-tube results

c = overgrowth by contaminant.
(c) + = positive before overgrown.
+ = one or two small colonies.
++ = several fair-sized colonies.
+++ = numerous colonies.
++++ = surface of medium covered with growth.

occasional shaking. In the morning of the next day eggs are freed from their shells and well mixed. Then the meat infusion is filtered through towelling, and the filtrate mixed with the egg in the proportion of one part of meat juice to two parts of egg by volume. These are thoroughly mixed, and then 1 per cent gentian-violet solution in 95 per cent alcohol is added to make a final proportion of 1:10,000. The mixture is tubed, slanted and coagulated at 95°C. for 1½ hours. Sterilize by inspissation for 1 hour at 75°C. on two successive days.

Medium of Sweany and Evanoff

To 450 gm. of finely ground veal add 377.5 cc. of sterile milk and 72.5 cc. of glycerin. Infuse over night in the ice-box with occasional shaking. The next day the filtrate is leached through gauze, and to the filtrate is added double the amount of fresh well-beaten eggs. Stir well, strain through gauze, tube and inspissate in slanted position for 1 hour at 90°C.; to sterilize, heat on two successive days for 1 hour at 75°C.

RESULTS

TABLE 2

Number of positives on various media

MEDIUM	PERIOD OF INCUBATION				
	2 weeks	3 weeks	4 weeks	5 weeks	6 weeks
Corper-Uyei	7	17	24	29	33
Dorset	1	3	5	10	15
Lubenau	1	5	8	10	18
Petragnani	7	11	17	21	27
Petroff	1	2	4	5	13
Sweany-Evanoff	0	1	5	8	13
Total on All Media	10	21	28	33	37

Total positives by microscopic examination = 33.
Total number of specimens = 42.

After six weeks' incubation the total number of positives obtained on the medium of Corper and Uyei equalled that of the microscopic method. In two cases this medium showed growth when the microscopic examination was negative; in two cases the stained smear was positive when the medium gave negative results. In only three cases did the Corper-Uyei medium fail to show positive results when other media were positive and in two of these contaminating overgrowths may have been the cause of failure. In three cases this medium showed growth when all other media failed. Colonies were frequently visible to the naked eye in two to three weeks, and almost always by the end of the fourth week. It was usually the first medium on which growth appeared and it often exceeded all others in luxuriance.

When planted on Dorset's medium the sediment of fifteen of the specimens gave positive results, compared with 33 microscopic positives. In 2 cases it was positive when the microscopic method was negative, but both of these positives were confirmed by other media.

Lubenau's medium proved to be the best of the egg media with the exception of the medium of Petragnani. After six weeks it gave 18 positive results. In 2 cases it was positive when the microscopic findings were doubtful; in one case it showed growth when the stained smear was negative.

Petragnani's medium gave very good results. After six weeks it showed 26 positives as against 33 by the microscopic method and the

Corper-Uyei medium. It was positive in 4 cases when the microscopic examination was negative, as well as in 2 cases when the stained smear gave doubtful results. In one case it was the only medium to show growth when the stained smear was negative for acid-fasts. Growth was usually luxuriant, and positives were nearly as rapid and frequent as on the medium of Corper and Uyei.

On Petroff's medium there were 13 positives after 6 weeks' incubation. In one case growth was positive when the microscopic method was negative, but other media also showed growth with this specimen. On this medium growth was sparse even when positives were recorded.

Like the Petroff medium the Sweany-Evanoff medium yielded 13 positives after 6 weeks. In the one case in which it was positive while the microscopic method was negative, as well as in the one specimen in which it was positive and the stained smear doubtful, growth was likewise observed on other media.

Whereas the microscopic method yielded 33 positives and 2 doubtful results, the total number of specimens found to be positive through the use of the culture tubes was thirty-seven. Of these, 36 were shown by the Corper-Uyei or Petragnani media, if the positives from these two are combined. In the first 6 specimens the practice of carefully pouring the homogenized sputum into a second centrifuge tube had not yet been adopted, and contaminations were all too frequent. Even here, however, the Corper-Uyei and Petragnani media showed more positives than the other media, the former medium having the least number of overgrowths by contaminants.

In view of Malkani's suggestion that the *S* type of organisms in a sputum may be isolated better by alkaline digestion and the *R* type by acid-digestion, it is interesting to note that several colony types were observed following treatment with sulphuric acid. This was particularly true of Petroff's medium, on which growth usually consisted of from 2 to 10 isolated colonies corresponding closely to the *R* and *S* types described in the literature, as well as intermediate forms. On the other media separate colonies were rare; as a rule, growth consisted of a heaped-up wrinkled mass which tended to cover the entire surface of the slant so that colony boundaries were indistinguishable. Occasionally a tube of one of the other media showed isolated colonies which resembled one or the other form.

SUMMARY AND CONCLUSIONS

In this study 6 media have been compared as to their relative value for the cultivation of the tubercle bacillus from sputum, following preliminary treatment of the 42 specimens with 6 per cent sulphuric acid according to the slightly modified Corper-Uyei method.

The medium of Corper and Uyei yielded the largest number of positives, being equal to the microscopic method in total number of positive results. Because of simplicity of preparation and the excellent results obtained through its use, this medium is particularly recommended for primary cultures of the tubercle bacillus following acid pre-treatment.

The medium of Petragnani is likewise highly recommended, since it yielded results nearly as good as those obtained with the Corper-Uyei medium. These two were superior to the other four media tried, in numbers of positives, at all times.

Lubenau's medium proved slightly superior to the media of Dorset, Petroff and Sweany-Evanoff, all of which gave practically the same results.

In this series the culture method has proved itself to be at least the equal of microscopic examination and, if anything, slightly superior to it. Out of 42 specimens examined, the microscopic method showed 33 positives while the culture tubes revealed 37 positives.

In the routine isolation of tubercle bacilli from sputa, it is recommended that both the medium of Corper-Uyei and that of Petragnani be employed.

Dissociation of the primary cultures into colonies resembling the so called *R* and *S* types has been noted particularly on Petroff's medium.

This work was carried out at the Massachusetts Institute of Technology, Cambridge, Massachusetts. My sincere thanks are due to Dr. Samuel C. Prescott, who extended the facilities of the Department of Biology and Public Health at the Institute, to the late Dr. Francis H. Slack for his help and advice throughout the experiment, and to Dr. Murray P. Horwood for his friendly criticism. I am indebted to Dr. P. F. Kelleher and Miss E. Conlon, both of the Cambridge Tuberculosis Hospital, through whose kindness the specimens were obtained.

BIBLIOGRAPHY

BLECHMANN, M.: C. Rend. Soc. Biol., 1927, xcvi, 1033.
BLUMENBERG, W.: Med. Klin., 1929, p. 1136.
BROWN, L., AND SMITH, D.: J. Med. Res., 1910, xxii, 517.
BURN, C. G.: Amer. Rev. Tuberc., 1922, vi, 950.
CORPER, H. J., FIALA, L., AND KALLEN, L.: J. Inf. Dis., 1918, xxiii, 268.

CORPER, H. J., AND UYEI, N.: Amer. Rev. Tuberc., 1927, xvi, 299; J. Lab. & Clin. Med., 1929, xiv, 393.
DESPEIGNES, V.: C. Rend. Soc. Biol., 1922, lxxxvi, 931.
DORSET, M.: Am. Med., 1902, iii, 555.
DSCHENG LI, B.: Beitr. z. Klin. d. Tuberk., 1930, lxxv, 367.
FRONGIA, E.: Giorn. di Batteriol. & Immunol., 1927, x, 705.
HAUPTMANN, W., AND BURTSCHER, J.: Wien. klin. Wchnschr., 1928, p. 84.
HOHN, J.: Münchn. med. Wchnschr., 1926, lxxiii, 2162.
JACOBI, A.: Klin. Wchnschr., 1927, vi, 2472.
KEILTY, R. A.: J. Exp. Med., 1915, xxii, 612.
LICHTENSTEIN, S.: Centr. f. Bakt., I. Orig., 1928, cviii, 239.
LIMOUSIN, H.: Ann. l'Inst. Past., 1921, xxxv, 558.
LUBENAU: Hyg. Rundschau, 1907, xvii, 1455.
MALKANI, M.: Amer. Rev. Tuberc., 1929, xix, 47.
MATTHIES, T.: Klin. Wchnschr., 1928, vii, 351.
MELLER, R.: Ztschr. f. Tuberk., 1927, xlviii, 137.
MOREAU, E.: Rev. d. l. Tuberc., 1922, iii, 381.
PAWLOWSKY, A. D.: Ann. l'Inst. Past., 1888, ii, 303.
PETRAGNANI, G.: Boll. Inst. Sieroterap. Milan, 1926, v, 173.
PETROFF, S. A.: J. Exp. Med., 1915, xxi, 38.
SANCHEZ, J. B.: Archiv. Inst. Nac. de Hiq. de Alfonso XIII, October 3, 1924.
SCHRADER, G.: Centr. f. Bakt., I. Orig., 1927, cii, 163.
SONNENSCHEIN, C.: Beitr. z. Klin. d. Tuberk., 1927, lxvii, 451.
STEWART, F. C.: J. Exp. Med., 1917, xxvi, 755.
SWEANY, H. C., AND EVANOFF, M.: Amer. Rev. Tuberc., 1928, xviii, 661.
TZETZU: Presse Méd., 1922, xxx, 503.
WOLTERS, K. L., AND DEHMEL, H.: Centr. f. Bakt., I. Orig., 1930, cxvii, 279 & 412.

A COMPARISON OF TISSUE REACTIONS TO PULMONARY INFECTION WITH TUBERCLE BACILLI IN ANIMALS OF VARYING RESISTANCE[1]

ARTHUR J. VORWALD

In tubercle-bacillus infection wide differences are seen in the native resistance of animals of various species, and an acquired resistance may modify an initial susceptibility. It is traditional that resistance and susceptibility to any disease are in part dependent upon the number and the types of cells that respond to the specific causative organism. This implies that individual variations in response to tubercle-bacillus infection are correlated with variation in cellular reaction in the tissues which harbor these bacilli.

To test this view, the native response of a variety of normal animals to equalized dosage of one and the same strain of tubercle bacilli at varying intervals after infection, was observed. Particular attention was paid to the following features: first, the localization and extent of the cellular reaction; second, the relation between the initial reaction and the subsequent course of the disease; and third, the character and number of cells taking part.

This study was confined to the reactions occurring in the lung. In spite of the relatively complex structure of this tissue, it is favorable for histological study of the response of the body to the tubercle bacillus, for several reasons. By intravenous injection of tubercle bacilli the traumatic lesions inseparable from all inoculations through direct puncture are avoided, and the lung acts as a filter for a very large part of the tubercle bacilli, so that primary tubercles are early formed and easily observed.

EXPERIMENTAL TECHNIQUE

Human-type tubercle bacilli (H37)[2] from a one-month-old culture were used. A weighed amount was triturated in a glass mortar until the mass

[1] From the Department of Pathology, University of Chicago, Chicago, Illinois.

[2] This was isolated at the Saranac Laboratory, Saranac Lake, in 1905 from the sputum of a patient with chronic ulcerative pulmonary tuberculosis, and it still possesses relatively high virulence for guinea pigs.

was reduced to a fine paste. After this, while grinding was continued, a drop of sterile normal saline solution was added from time to time until the paste was evenly dispersed. This suspension was then made up to the desired dilution (0.1 mgm. per 1 cc.), placed in a glass-stoppered bottle, and shaken gently to bring about a more even distribution of the bacilli. Samples were examined microscopically to ensure that the organisms were well distributed and that clumping was reduced to a minimum.

An intravenous injection of a standard dose (0.1 mgm. per kilogram body weight) of this suspension was made into a series of normal guinea pigs, monkeys, dogs, rabbits, rats, chickens and cats. At intervals of one day, one week and one month after injection, an animal of each species was killed, and the lungs fixed *in situ* by an intratracheal injection of Zenker's fluid. Serial sections, to be used for the study of the localization and extent of the cellular reaction, were cut in paraffin and stained with carbol-fuchsin for the tubercle bacilli. The nuclei were stained with dilute haematoxylin. For the cellular differentiation, tissues were imbedded in celloidin and sectioned. The tubercle bacilli and nuclei were stained in the same manner as in the paraffin sections. The counterstains used were methyl-green in one series of slides, and eosin-azure in the other. In still another series, for contrast between the eosinophilic granules and the red-staining tubercle bacilli, orange G-azure was used.

THE LOCALIZATION OF THE CELLULAR REACTIONS

Krause, throughout all his papers on tuberculosis, has assigned a position of prime importance to the lymphoid tissue as a point of localization. He contends (1) that it is because of the unequal amount of this lymphoid tissue in the lungs of the rabbit and of the guinea pig that these two animals differ in the amount of pulmonary tuberculosis which they ultimately develop. The guinea pig develops much less lung tuberculosis because it is relatively poor in intrapulmonic lymphoid tissue, while the rabbit develops much more because it is rich in intrapulmonic lymphoid tissue. Krause has correlated this fact with the localization of tuberculous lesions in the lung of the child and of the adult, the childhood type being analogous to that of the guinea pig, and the adult type to that of the rabbit. Baldwin, Petroff and Gardner (2) are of the same opinion, that is, that the first tubercle, whatever the pathway of infection, develops within masses of lymphoid tissue. Rich (3) opposes this idea

in saying that "there is very good evidence that the normal lymphatic anatomy of the human lung at different age periods is of little importance in determining the distribution or character of tuberculous involvement or the degree to which the regional lymph nodes will be involved."

In the experiments here reported the early reactions in the guinea pig, monkey, rabbit, rat, chicken, and cat did not occur in strict relation to the above-mentioned structures. There was a beginning thickening of the alveolar walls by cells, which by their later increased accumulation and growth involved these structures. In the dog, on the other hand, the initial response occurred principally about the blood-vessel wall and in its progression narrowed the lumen of the vessel. This reaction may have taken place in the perivascular lymphatics, but there was little or no localization in the larger perivascular lymphatic aggregates. Krause (4) states that the localization in the lungs depends upon the number of the bacilli injected, and upon the concentration at any one place of quantities of bacilli that completely plug channels which carry particles out of the lung. In this experiment these factors seem to have been controlled. Embolization by bacterial masses was reduced to a minimum by adequate trituration of the bacilli in preparation of the suspension. Although the injection of 0.1 mgm. per kilogram body-weight would be a large local dose, such an amount when injected into the blood-stream, as in this experiment, is quickly dispersed and very small numbers become localized at one point.

It is not the purpose here to deny the fact that lymphatics play a rôle in primary tuberculous infection. There is sufficient data to support the view that foreign particles coming to the lung do enter the domain of the lymphatic channels and are concentrated in the major lymphatic agglomerates. Inert foreign particles, mainly in the form of suspensions of ink, and also suspensions of live coccoid bacteria have been injected into the animal body and their distribution throughout the tissues verified by numerous postmortem examinations. Lurie (5), in determining the fate of intravenously injected tubercle bacilli in the organs of rabbits, reports that the localization of the bacilli follows the distribution of particulate matter, but the relative position of the lung as a point of localization is still doubtful. With the tubercle bacillus, because of its morphology, the distribution may not be in strict accordance with that of small round carbon particles or coccoid bacteria. A mechanical factor, such as the relation between the tubercle bacillus and the calibre of the capillary lumen through which it is passing and the speed of progression through that lumen may possibly determine its localization.

Werigo (6), in studying the early reaction of the rabbit's tissues to the anthrax bacillus, recognized the importance of this mechanical factor where he says, "It seems very likely that this phagocytosis takes place by preference in the capillaries of the lungs where the bacteria, especially such large bacteria as the anthrax bacillus, can easily stop for some moments. Thanks to the mechanical causes."

Besides this mechanical factor a biological factor plays a rôle in the primary localization of tubercle bacilli. Just as with other organisms, so too with the tubercle bacillus there is an early interplay between the tissue constituents and the bacillus. This latter factor has been observed by Borrel (7), Weil (8) and by Vorwald (9) (10) in the earlier cellular reaction to tubercle bacilli injected intravenously into normal rabbits. The author (10) has shown that one hour after infection there was a definite polymorphonuclear leucocytic response with extensive phagocytosis of the bacilli by these cells. Subsequently the bacillus was usually carried by this phagocytosing cell into the alveolar-wall tissue, the lymphatics, or the alveolar space; in other cases the cell with its content remained localized in the capillary lumen.

The efficiency of the lungs as a filter for the injected tubercle bacilli was better realized by gross and microscopic observation of other tissues such as the liver, and kidneys of the respective animals. Examination of serial sections of these organs by Harms (11) revealed a decided decrease, when compared with the lungs of the same animals, in the number of stainable tubercle bacilli and in the extent of the cellular reactions to these bacilli.

The reason for the preponderance in the lung involvement in the animals of this series, particularly at the one-month period, may in part be due to the fact that that organ is better adapted for the multiplication of the bacilli. Corper, Lurie and Uyei (12) have suggested that, because of the higher oxygen tension of the alveolar air, the bacilli grow much more rapidly in the lung than in any other organ of the body. A series of experiments are being conducted in this department, at the present time, to determine the effect of massive atelectasis by bronchial stenosis in dogs on experimentally produced pulmonary tuberculosis in that animal. The results, thus far, indicate that the mechanism hypothecated by Corper and his associates is a factor of major importance in determining the progression of tuberculous lesions in the lung tissue.

There may be still other factors to explain the predominance of pulmonary tuberculosis, such as manner of introduction and nutritional requirements. In any event, the ability of the lungs to retain a major portion

of the tubercle bacilli injected intravenously is a factor of paramount importance in determining the early localization of the tubercle.

The lymphoid tissue, although not serving as a focus for early localization of the acid-fast bacilli, did show some change. It became increasingly more prominent in the one-week and the one-month periods, at which time it showed hyperplasia and numerous mitotic figures. Thus it seemed that tubercle bacilli, even though not present in the lymphoid foci, exerted a stimulating influence upon them bringing about a decided hyperplasia of their constituent elements. Maximow, commenting on this phenomenon in inflammation, expressed the opinion that it was such lymphoid foci that gave rise to the lymphocytes and thus, in part, to the polyblasts of lymphocytic origin appearing in the field of inflammation.

EXTENT OF CELLULAR REACTION

The volume of the cellular reaction in the lung tissue was determined by microscopic observation of serial sections. A number of representative reactions about tubercle bacilli, in each of the animals at the different periods, was followed through the sections from beginning to end, and in each case measured by means of a Filer screw-micrometer ocular. The tubercle in the majority of cases varied in shape, being often circular, ovoid, or extending through the tissues in a linear fashion. In order, therefore, to secure the average diameter of the cellular reaction it was necessary to take various measurements, first through its least and then through its greatest thickness. By averaging these measurements an approximation of the diameter of a corresponding circular reaction was obtained. By measuring thus the cellular reaction in each section through which the tubercle in question extended, and then by obtaining the total of these diameters and dividing it by the number of sections in which the reaction appeared, an average diameter for the whole tubercle resulted. In this manner the average diameter of from five to ten tubercles in each animal at each period was obtained. The results are recorded in table 1, and in chart 1 which is a graphic representation of the measurements obtained. The following facts should be noted in connection with it.

In the cat, at the one-day period, there were in the alveolar walls many isolated cells which had phagocytosed one or more tubercle bacilli. About these cells there was no reaction of the lung tissue and consequently no measurement could be obtained.

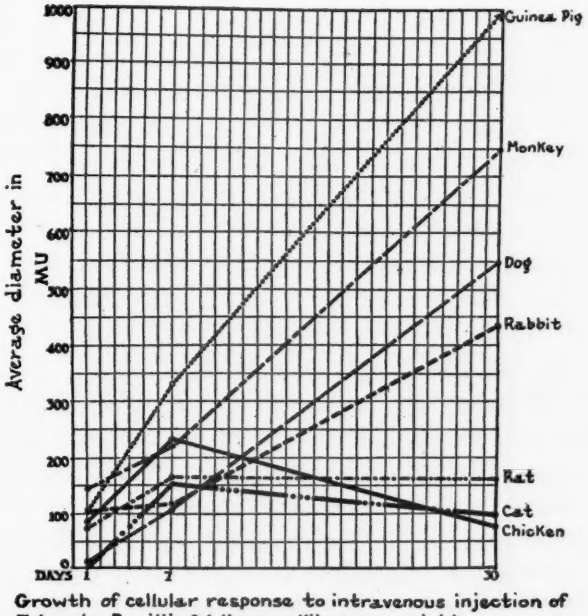
The dog at the same period responded with a slight perivascular accu-

mulation of cells not measurable in any way conforming with the rest of the series. However, to indicate that there was a reaction at the one-day period the cellular growth has been raised slightly above the zero point

TABLE 1

ANIMAL	AVERAGE SIZE AT ONE DAY	AVERAGE SIZE AT ONE WEEK	AVERAGE SIZE AT ONE MONTH
	mm	mm	mm
Guinea pig	105	325	diffuse growth
Monkey	141	223	746
Dog	*	109	548
Rabbit	105	119	434
Rat	74	163	160
Chicken	83	235	76
Cat	*	152	94

* Too limited to be measured.



Growth of cellular response to intravenous injection of Tubercle Bacilli. 0.1 Mg. per Kilogram weight.

CHART 1

on the graph. At the one-week period the cellular reactions to the tubercle bacilli were still confined to the tissue immediately surrounding the blood-vessels, with no definite tubercle-formation. In order to measure

the extent of this cellular reaction it was necessary, first, to obtain the mean diameter of the blood-vessel and to subtract this from the mean diameter of the perivascular reaction including the blood-vessel. Thus the average diameter of the cellular reaction was obtained.

From observation of the chart, it appears that the reaction in the monkey at the end of one day surpasses that of all other animals at the same period. This was, however, the measurement of but one cellular response, the only reaction observed in the considerable number of sections examined. Many isolated cells were indeed found which had phagocytosed tubercle bacilli. These cells lay free in the lumen of blood capillaries and also in the alveolar walls. There was no reaction about them. The difficulty in evaluating the extent of response is obvious and for this reason the measurements of the single reaction were recorded. It thus does not represent an average of several diameters, as in the case of the other animals at this period.

The extent of the individual cellular reaction of the rat at the one-week and the one-month periods was recorded as practically the same. It might therefore appear that in this animal there was no progression of the disease. However, at one month there was a larger number of isolated cellular accumulations per given lung area than at one week, the ratio being as two to one. If the total volume of lung tissue involved were taken into consideration in the graph, progression at the later period would certainly be indicated.

The guinea pig at the end of one month responded not with isolated cellular accumulations but rather by a diffuse involvement of the whole lung tissue. The true curve representing the growth at this period should perhaps rise more sharply than indicated.

From the foregoing table and chart it is apparent that the extent of the response in the various species of animals is decidedly different. The ultimate outcome of the disease in the guinea pig and monkey on the one hand, and the rat and the chicken on the other, agrees quite well with the established ideas regarding the great susceptibility of the former group and the decided resistance of the latter two animals to human-type tubercle-bacillus infection. The final outcome of the disease in the rabbit also coincided with the general opinion that rabbits are less susceptible (more resistant) to human-type tubercle-bacillus infection than either the guinea pig or monkey. This inequality in reaction serves as a basis for routine differentiation of human- and bovine-type tubercle bacilli. With the other animals, however, such as the dog and the cat, study of experimental tubercle-bacillus infection has been less extensive than with

the previously mentioned species. There are scattered reports of spontaneous infection in dogs and cats. Fox (13) states that "tuberculosis occurs among domestic carnivores with reasonable frequency (3–5 per cent among dogs and 0.2–2 per cent among cats)." The opinion is prevalent that both the dog and the cat are relatively resistant to human-type tuberculosis. This study indicates, however, that our idea regarding the resistance of dogs to tubercle bacilli has been exaggerated. As recorded in the chart the dog's response at the one-month period was less than that of the very susceptible monkey but more than that of the moderately resistant rabbit.

The data presented are at some variance with other long and thorough investigations on the relation between the initial cellular reaction and the subsequent course of the disease. Krause (14), after pointing out that "there can be no virulence of germ without a corresponding susceptibility of animal," raises the question "are animals natively susceptible to virulent tubercle bacilli because their tissues are congenitally incapable of meeting first infection with promptness which is necessary to localize the germ?" and asks "Is it possible that the quality of virulence of germ is proportional inversely to the ability of tissue to react to it?" Krause (15) and Willis (16) explain the heightened resistance of the previously infected animal to a second infection on the ground that tubercle bacilli introduced into the body of an infected animal appear to be promptly localized by allergic reaction at the point of inoculation.

According to this view the outcome of the disease would presumably depend upon the extent of the initial cellular response, and one would expect those animals whose initial reaction is very meagre to develop the greatest amount of tuberculosis. This was, however, not the case. Such animals as the cat, the rat and the chicken whose early reactions were small, at the one-month period also showed the least tuberculosis. The guinea pig and monkey, on the other hand, reacted intensely within the first week, and a month later showed massive tuberculosis. The guinea-pig and the rabbit responses at the end of one day were very acute, and these animals should, therefore, according to the view cited, be relatively resistant. The guinea pig, however, proved the most susceptible animal of the group, while the rabbit was relatively more resistant than either the guinea pig, monkey or dog. The dog, whose early reaction was slightly in excess of that of the cat, developed much more tuberculosis ultimately.

This indicates that the individual variations in susceptibility of animals to tubercle bacilli are not dependent upon the initial cellular reaction.

One cannot, therefore, by observation of the early reaction of tissue cells to the bacilli, forcast the outcome of the disease.

CELLULAR DIFFERENTIATION

In the regions of inflammatory reaction certain types of cells, namely, polymorphonuclear leucocytes and typical lymphocytes and monocytes, were easy to identify. In the case of a larger number of cells, however, classification was not as simple. Mononuclear cells of varying appearance, with some characters in common with typical differentiated monocytes and with lymphocytes, but different in important respects from either, made up a large portion of the reacting mass in most tubercles. Cells of this group have been variously identified by observers as modified monocytes, clasmatocytes, histiocytes, polyblasts, etc. Much of the distinction has been based upon supravital staining, a method not applicable here, where the relation of the tubercle to previous anatomical structure was to be observed. It was, therefore, decided, for the time being, to include them all under the term mononuclear exudate cells, giving in each case an accurate description of the predominant type as they appeared in sections counterstained with eosin-azure. Differential counts for the whole series of animals follow.

Guinea pig

TABLE 2

PERIOD	ONE DAY	ONE WEEK	ONE MONTH
	per cent	*per cent*	*per cent*
Total mononuclear exudate cells	45.6	48.7	53.4
Mononuclear exudate cells with tubercle bacilli	5.6	4.8	7.6
Typical differentiated monocytes	0.7	0.9	0.3
Lymphocytes	12.3	12.0	3.7
Plasma cells	0	0	0
Total polymorphonuclear neutrophilic* leucocytes	34.3	29.3	32.5
Polymorphonuclear neutrophilic* leucocytes with tubercle bacilli	5.5	7.1	17.3
True eosinophiles	0.9	0.7	0
Mitotic figures	0.6	0.4	0
Undetermined	5.1	5.7	4.3

* Pseudo-eosinophiles.

At one day the reactions consisted of well-localized thickenings of the alveolar septa by cells, with but slight exudation into the alveolar spaces. At one week the cellular accumulations had increased in size so that the septa were thickened for great distances and the air spaces were practically obliterated. By one month the reacting cellular mass had increased in size to such an extent that tubercles previously well isolated were beginning to coalesce. The alveolar spaces were now obliterated. There was no longer typical isolated tubercle-formation but rather a uniform involvement of the whole lung tissue, making measurements of individual reactions impossible. The majority of cells reacting throughout all periods were of the mononuclear-exudate type. Polymorphonuclear neutrophilic leucocytes (pseudo-eosinophiles), however, were prominent in all stages. Most of them lay in the alveolar spaces. There were numerous instances in which a cell of this type with its phagocytosed tubercle bacillus had been engulfed by a large mononuclear-exudate cell. The tubercle bacilli were everywhere within cells and in the later stages concentrated in the neutrophiles.

Monkey

TABLE 3

PERIOD	ONE DAY*	ONE WEEK	ONE MONTH
		per cent	*per cent*
Total mononuclear exudate cells		29.1	60.5
Mononuclear exudate cells with tubercle bacilli		5.4	3.7
Typical differentiated monocytes		0.2	0.2
Lymphocytes		9.8	23.4
Plasma cells		0	0.7
Total polymorphonuclear neutrophilic leucocytes		51.2	9.8
Polymorphonuclear neutrophilic leucocytes with tubercle bacilli		8.9	0
True eosinophiles		0	0
Mitotic figures		1.3	0.4
Undetermined		8.0	4.8

* See page 279.

At one day only one cellular reaction was observed and this in a paraffin section not stained for differentiation of cells. In a great many other

serial sections, made from stock at hand, no such reaction was observed. Instead, many isolated cells containing tubercle bacilli were found; however, there was no accompanying cellular reaction about them. Differentiation of these cells obtained from numerous eosin-azure stained sections is as follows:

Mononuclear exudate cells in the alveolar walls containing tubercle bacilli, 13
Monocytes in the blood-stream containing tubercle bacilli, 6
Polymorphonuclear leucocytes containing tubercle bacilli, 8
Mitotic figures in the blood-stream, 4

At one week cellular accumulations were easily observed. The alveolar septa showed isolated thickenings by cells and the neighboring alveolar spaces contained cells which lay free or grouped in small masses. The majority of cells making up the reaction at this period were polymorphonuclear neutrophilic leucocytes and the tubercle bacilli were confined mainly to these cells, but to a lesser degree were present in the reacting mononuclear-exudate cells. Just as in the guinea pig, so too in this animal many of the polymorphonuclear neutrophilic leucocytes with their phagocytosed tubercle bacilli were engulfed by mononuclear-exudate cells. Caseation at this one week period had not as yet taken place, but degeneration of cells was observed, especially of those collected in masses within the alveolar spaces. At one month there was typical tubercle-formation with central caseation. The caseating area contained much nuclear debris and great numbers of pycnotic mononuclear cells and degenerating polymorphonuclear leucocytes which could not be differentiated with certainty. The mononuclear exudate cells, now epithelioid, were larger than in the previous stages, and possessed round, eccentric nuclei poor in chromatin, and a granular eosinophilic and slightly foamy cytoplasm. The lymphocytes and plasma cells were concentrated about the periphery of the tubercle. The tubercle bacilli at this stage were concentrated in and about the caseating centre.

Dog

TABLE 4

PERIOD	ONE DAY*	ONE WEEK	ONE MONTH
		per cent	*per cent*
Total mononuclear exudate cells		74.7	77.8
Mononuclear exudate cells with tubercle bacilli		0.3	13.1
Typical differentiated monocytes		0.5	0

TABLE 4—*Concluded*

PERIOD	ONE DAY*	ONE WEEK	ONE MONTH
		per cent	*per cent*
Lymphocytes		7.4	9.9
Plasma cells		1.6	1.3
Total polymorphonuclear neutrophilic leucocytes		11.2	5.4
Polymorphonuclear neutrophilic leucocytes with tubercle bacilli		0	0
True eosinophiles		0	0
Mitotic figures		0.9	4.7
Undetermined		3.4	0.6

* See page 281.

At one day the reactions consisted of slight perivascular accumulations of cells. In the many sections examined only two tubercle bacilli were observed. At one week there was a decided increase in the size of the individual perivascular accumulations. This increase was due mainly to mononuclear-exudate cells, about 50 per cent of which had a chromatin-rich nucleus with a slightly foamy basophilic cytoplasm. The remainder had larger and clearer nuclei with distinct nucleoli and pale blue foamy cytoplasm. At one month the reactions were concentrated about the much-compressed blood-vessels and the smaller respiratory bronchioles. There was no evidence of caseation. The tubercle bacilli in the earlier stages were absent or very difficult to find. At one month they were prominently distributed throughout the cells making up the cellular reaction.

Rabbit

TABLE 5

PERIOD	ONE DAY	ONE WEEK	ONE MONTH
	per cent	*per cent*	*per cent*
Total mononuclear exudate cells	72.0	74.2	63.1
Mononuclear exudate cells with tubercle bacilli	2.2	4.4	0.4
Typical differentiated monocytes	0	0	0
Lymphocytes	2.2	9.3	17.2
Plasma cells	0	0.4	8.6

TABLE 5—*Concluded*

PERIOD	ONE DAY	ONE WEEK	ONE MONTH
	per cent	*per cent*	*per cent*
Total polymorphonuclear neutrophilic* leucocytes	14.3	10.4	5.0
Polymorphonuclear neutrophilic* leucocytes with tubercle bacilli	2.2	1.1	0.2
True eosinophiles	0	0.3	0
Mitotic figures	0.1	0.1	0.07
Undetermined	11.3	4.6	5.8

* Pseudo-eosinophiles or "specials."

At one day the interalveolar septa were in places markedly thickened, by cells mainly of the mononuclear-exudate type and to a lesser degree by polymorphonuclear leucocytes. At one week the picture did not deviate appreciably from that of one day except that there was more filling up of the air-spaces by cells of the mononuclear exudate type. At one month there was definite tubercle-formation with central caseation, enclosed by cells (mononuclear-exudate cells), whose nuclei were mainly ovoid and whose cytoplasm was eosinophilic and slightly foamy. These were typical epithelioid cells. About the periphery of the tubercle, lymphocytes and plasma cells were especially concentrated.

At the one-day period the tubercle bacilli were about equally phagocytosed by mononuclear-exudate cells and polymorphonuclear leucocytes (pseudo-eosinophiles). In many instances these pseudo-eosinophiles and their phagocytosed bacilli had been engulfed by mononuclear-exudate cells. Very often such phagocytosed cells showed dispersion of cytoplasmic granules and pycnosis of nuclei, leaving the tubercle bacilli lying in a clear space in the cytoplasm of the engulfing cell. At one month there was a decided increase in the number of observed bacilli per tubercle, and the bacilli were mainly concentrated in and immediately around the caseous centres.

Rat

TABLE 6

PERIOD	ONE DAY	ONE WEEK	ONE MONTH
	per cent	*per cent*	*per cent*
Total mononuclear exudate cells	74.6	78.5	78.8
Mononuclear exudate cells with tubercle bacilli	4.1	17.6	17.4

TABLE 6—*Concluded*

PERIOD	ONE DAY	ONE WEEK	ONE MONTH
	per cent	*per cent*	*per cent*
Typical differentiated monocytes	9.5	2.4	4.1
Typical differentiated monocytes with tubercle bacilli	4.1	0	0
Lymphocytes	5.4	9.2	10.0
Plasma cells	0	0	0
Total polymorphonuclear neutrophilic leucocytes	8.1	5.2	1.6
Polymorphonuclear neutrophilic leucocytes with tubercle bacilli	1.3	0.4	0
True eosinophiles	0	0.1	0
Mitotic figures	0	1.2	1.6
Undetermined	2.05	2.9	2.7

At one day the cellular accumulations were confined principally to the alveolar walls, with little exudation into the alveolar spaces. The walls were thickened for the most part by mononuclear-exudate cells. At one week and one month there was more obliteration of the alveolar spaces by mononuclear-exudate cells which possessed centrally placed, round nuclei with distinct nucleoli. The cytoplasm was basophilic and not foamy. Others of these cells were larger and their cytoplasm was very foamy. At one month the tubercles, although approximately the same in size as those at the one-week period, were at this later stage more numerous. The tubercle bacilli were within mononuclear-exudate cells, mainly of the type with a basophilic nonfoamy cytoplasm. Others, however, were engulfed by the foamy type of cell, but decidedly in less number.

Chicken

TABLE 7

PERIOD	ONE DAY	ONE WEEK	ONE MONTH
	per cent	*per cent*	*per cent*
Total mononuclear exudate cells	77.7	78.5	87.0
Mononuclear exudate cells with tubercle bacilli	2.3	3.6	0
Typical differentiated monocytes	0.4	0.3	0
Lymphocytes	7.1	11.6	13.0
Plasma cells	0	0	0

TABLE 7—*Concluded*

PERIOD	ONE DAY	ONE WEEK	ONE MONTH
	per cent	*per cent*	*per cent*
Total polymorphonuclear neutrophilic* leucocytes	9.1	6.1	0
Polymorphonuclear neutrophilic* leucocytes with tubercle bacilli	0	0	0
True eosinophiles	0.2	0	0
Mitotic figures	0	0.1	0
Undetermined	5.2	3.1	0

* Spindle-shaped "crystalloid" eosinophiles.

The main type of cell throughout all periods was the mononuclear-exudate cell. At one day most of this type contained clear, slightly eccentric, irregular nuclei with a lining net-work which was attached to one, two or three distinct nucleoli. The cytoplasm stained pale blue and was not foamy. These cells were occasionally massed together, forming small but typical Langhans-type giant cells. At one week these mononuclear-exudate cells formed the centre of the tubercle. In general, they possessed more centrally placed, clearer nuclei and distinct nucleoli. The cytoplasm was faintly eosinophilic, and appeared granular and very slightly foamy. Lymphocytes penetrated this group of cells and surrounded the entire tubercle. At one month the tubercles were very much smaller and difficult to find. They consisted of a very compact group of mononuclear-exudate cells whose nuclei were similar to those at the one-week period. Their cytoplasm, however, was slightly granular and eosinophilic. At both the one-week and one-month periods there was degeneration but no frank caseation. The tubercle bacilli at one day were localized in groups of from ten to thirty in two or three mononuclear cells. At one week they were more evenly distributed but difficult to find. At one month they were absent.

Cat

TABLE 8

PERIOD	ONE DAY	ONE WEEK	ONE MONTH
	per cent	*per cent*	*per cent*
Total mononuclear exudate cells	48	53.8	86.7
Mononuclear exudate cells with tubercle bacilli	48	0.1	0.2

TABLE 8—*Concluded*

PERIOD	ONE DAY	ONE WEEK	ONE MONTH
	per cent	*per cent*	*per cent*
Typical differentiated monocytes with tubercle bacilli	52	0	2.6
Lymphocytes	0	4.5	3.7
Plasma cells	0	0	0
Total polymorphonuclear neutrophilic leucocytes	0	36.8	4.7
Polymorphonuclear neutrophilic leucocytes with tubercle bacilli	0	0	0
True eosinophiles	0	0.3	0
Mitotic figures	0	0.1	0.4
Undetermined	0	4.2	1.6

At one day there was no cellular reaction. Tubercle bacilli were found in occasional mononuclear cells, the majority of which were in the capillary lumen of the alveolar walls. These cells were differentiated as monocytes. The tubercle bacilli engulfed by such cells usually lay in a clear vacuole in no relation to the indentation of the nucleus. Others of these mononuclear cells lay in the alveolar walls and could not be differentiated as monocytes. They have been classified in table 8 as mononuclear-exudate cells. At one week and one month distinct cellular accumulations (small tubercles) were observed, which at the later period were smaller and fewer in number than at the one-week period. The tubercle bacilli at all stages were very difficult to find. At the later periods the small tubercles rarely contained a single bacillus and never more than one.

These data indicate that the cellular response in all animals at one day, one week and one month consisted mainly of mononuclear-exudate type cells. From observation of the nuclear and cytoplasmic structure and the relation between the two, it appeared that, in general, the mononuclear-exudate cells in the response at the earlier period differed somewhat from those partaking in the later reactions. At one day these cells in all animals varied in size and possessed eccentric, irregular, chromatin-rich nuclei and distinct nuclear walls. The cytoplasm stained a uniform pale blue with the eosin-azure technique and was not foamy. At one week the majority of mononuclear-exudate cells in the response of the guinea pig, rabbit, rat, and to a less extent the dog, were more uniform

in size, morphology and staining characteristics. In the chicken and the cat these cells possessed a larger, more ovoid, chromatin-poor nucleus with distinct nucleoli and nuclear walls. The cytoplasm was slightly foamy, with increased eosinophilia in those of the chicken. The exudate cells of the monkey, at this period, had a distinct foamy, slightly eosinophilic cytoplasm. This was also true for about half of those responding in the dog. At one month in the guinea pig, monkey, dog and rabbit the responding mononuclear cells had a large, more ovoid, chromatin-poor nucleus with distinct nucleoli. The cytoplasm was now foamy and moderately eosinophilic. Those of the cat were similar in type, except that they possessed a slightly more foamy cytoplasm. In the chicken the cytoplasm became more granular and eosinophilic. The rat responded with a type whose nuclei were chromatin-rich and slightly irregular and whose cytoplasm was both foamy and nonfoamy.

Sabin, Doan and Cunningham (17) in 1925 discriminated by supravital technique between two main types of mononuclear cells, the monocyte and the clasmatocyte. They advanced the hypothesis at that time that the monocytes retained the tubercle bacillus intact and afforded it opportunity to survive and multiply over long periods of time, while the clasmatocytes destroyed the bacillus. Sabin (18) and her coworkers consider the monocyte the source of the specific epithelioid cell of the tubercle.

Lewis (19), however, has shown by tissue culture that macrophages (clasmatocytes) become transformed into typical epithelioid cells. Hetherington and Pierce (20), also from tissue-culture experiments, have concluded that monocytes become transformed into clasmatocytes and that clasmatocytes in turn become epithelioid cells and Langhans-type giant cells. More recently Sabin (21) has stated that clasmatocytes and monocytes are very closely allied functional strains with many characteristics in common, and that it is possible for the monocyte to become a clasmatocyte. Gottlieb (22) has presented evidence to show that the tubercle bacillus is gradually digested in the cytoplasm of the monocyte. He looks upon the monocytic reaction in tuberculous infection as an attempted protective mechanism.

If Sabin, Doan and Cunningham's original hypothesis is correct one might expect that, in those animals, such as the guinea pig and monkey, which are very susceptible, the cellular reaction would be mainly of the monocytic type, while in the rat and chicken, animals more resistant, the clasmatocytic type of cell would be preponderant.

The supravital method was attempted in this experiment by a study of scrapings of the lung tissue. The inability, however, to obtain a preparation consisting of the cells of a tubercle, which in most animals, particularly at the early periods, was grossly not visible, made this method impracticable for a study of the cells making up the cellular reaction.

With fixed tissue stained by eosin-azure, the mononuclear-exudate cells making up the early stages of response in the various animals resembled somewhat the monocytes resting in the lumen of blood-vessels. In general, however, they were much larger than typical monocytes, their nuclei less rich in chromatin, and their cytoplasm less basophilic and more foamy. In the later stages there was no apparent similarity between the majority of mononuclear-exudate cells responding and typical monocytes. They possessed too many variations in nuclear and cytoplasmic structure and relationship. It was this latter fact that prompted Maximow to give the cells of this character the name *polyblasts*. He applied it because of the diversity of their appearance and their transformations. He believed that they arose mainly from transformed lymphocytes and monocytes of the blood-stream, and also in smaller part from the tissue cells *in situ*. If all these cells arose from fixed-tissue cells, then one might expect to find numerous cells undergoing mitotic division. In all observations of tissue of animals at the various stages the infrequency of mitotic figures in the field of inflammation was striking. This tends to support Maximow's contention that the majority of cells come from the blood-stream, unless extensive and rapid division by amitosis be admitted.

The polymorphonuclear neutrophilic leucocytes in the earlier stages were prominent in all animals except the dog and cat. In the remaining animals they played a major rôle in the phagocytosis of the tubercle bacilli, notably so in the guinea pig and the rabbit. These latter two animals responded in the beginning with large accumulations of polymorphonuclear leucocytes, which increased in the later stages in the guinea pig, but decreased in those of the rabbit. The striking persistence of these cells, in those animals which are most susceptible, namely, the guinea pig, the monkey and the rabbit, has some significance. Their rôle in tuberculosis has been particularly stressed by Medlar (23), and Medlar and Kastlin (24), who have emphasized their late appearance, with the onset of caseation, and correlated it with defeat of the host. In the experiment here reported the most susceptible animal, the guinea pig,

showed a persistent and slight increase in the number of polymorphonuclear leucocytes partaking in the reactions at the successive periods; true caseation, however, never resulted. In the monkey and the rabbit, caseation was present at the one-month period, but there was at this time a decided decrease in the number of polymorphonuclear leucocytes partaking in the individual responses, except perhaps in the caseating centre of the monkey's tubercle, where these cells could not be differentiated with certainty. In the chicken, on the other hand, a most resistant animal, degeneration and very slight caseation occurred at the one-week and one-month periods; there was throughout all stages a minimum polymorphonuclear leucocytic reaction. In the dog, rat, and cat caseation never occurred and the polymorphonuclear leucocytic response in all cases, except the cat at the one-week period, was always quite meagre. In brief this study indicates that the polymorphonuclear leucocytes appear early in the reaction, play a rôle in the localization of the bacilli, persist in the reaction of the most susceptible animals, and bear no definite relation to the process of caseation.

SUMMARY

Human-type tubercle bacilli in the proportion of 0.1 mgm. per kilogram body-weight were injected intravenously into guinea pigs, monkeys, dogs, rabbits, rats, cats and chickens. In all cases the lung tissue, in contrast to the intrapulmonic lymphoid tissue, retained a major portion of intravenously injected tubercle bacilli, and the initial cellular reaction occurred at the point of lodgment of the organisms. The lymphoid structures of the lung were involved only secondarily.

The susceptibility of the animals studied, as indicated by the measured extent of the individual cellular reactions, showed decided variations. The guinea pig and the rabbit, although in the beginning responding with an equally intense reaction, ultimately differed greatly as to the amount of tuberculous tissue developed. The guinea pig at one month proved to be a most susceptible animal, and the rabbit a much more resistant one. The rat and the chicken on the other hand, responding early with a reaction slightly less than that in the guinea pig and rabbit, at one month showed decidedly more resistance. The monkey (see pp. 279 and 280) and dog, which at one day showed a minimal response, less than that in any of the aforementioned animals, at the final period proved to have less extensive tuberculous reaction than the guinea pig, but much more

than the rabbit, rat, or chicken. The cat, the remaining animal of the series, reacted most sluggishly in the beginning, but, unlike the monkey and dog, in the final outcome proved a most resistant animal. The variations in susceptibility therefore did not parallel the intensity of the initial cellular reaction.

In the guinea pig, rabbit and rat the polymorphonuclear neutrophilic leucocyte played an important part in localizing the tubercle bacilli. Subsequently these leucocytes with their bacillary content were commonly phagocytosed by large mononuclear exudate cells. In the more mature reactions the mononuclear-exudate cell was the predominant type in all animals. The differentiation of these cells, in fixed tissues stained with eosin azure, into monocytes and clasmatocytes could not be made. No relation was detected between these mononuclear-exudate cells and the susceptibility to tuberculosis of the individual species studied.

There was an evident quantitative and also a qualitative difference in species reactivity, a quantitative one as shown by the difference in size of the cellular responses, a qualitative one in that in certain species polymorphonuclear leucocytes persisted in the responses throughout all periods. In other species these cells took very little part in the later reactions, and in the chicken, a resistant animal, they were absent in the response at the one month period.

No constant relationship was found between caseation and any particular type of cellular reaction.

REFERENCES

(1) KRAUSE, A. K.: Amer. Rev. Tuberc., 1922, vi, 1.
(2) BALDWIN, E. R., PETROFF, S. A., AND GARDNER, L. S.: Tuberculosis, bacteriology, pathology and laboratory diagnosis, 1927.
(3) RICH, A. R., AND MCCORDOCK: Bull. John's Hopkins Hospital, 1929, xliv, 237 & 424.
(4) KRAUSE, A. K.: Amer. Rev. Tuberc., 1926, xiv, 271.
(5) LURIE, M. B.: Jour. Exper. Med., 1928, xivii, 155.
(6) WERIGO: Ann. de l'Inst. Pasteur, 1894, viii, 1.
(7) BORREL, A.: Ibid., 1893, vii, 593.
(8) WEIL, J. A.: Ann. Méd., 1931, xxx, 444.
(9) VORWALD, A. J.: Arch. Pathol., 1931, xii, 143.
(10) VORWALD, A. J.: Amer. Rev. Tuberc., 1932, xxv, 74.
(11) HARMS, H. P.: Personal communication.
(12) CORPER, H. J., LURIE, M. B., AND UYEI, N.: Amer. Rev. Tuberc., 1927, xv, 65.
(13) FOX, H.: Ibid., 1928, xvii, 435.
(14) KRAUSE, A. K.: Ibid., 1922, vi, 223.
(15) KRAUSE, A. K.: Ibid., 1917, i, 65 (and many other publications).

(16) WILLIS, H. S.: Ibid., 1925, xi, 439.
(17) SABIN, F. R., DOAN, C. A., AND CUNNINGHAM, R. S.: Contributions to Embryology, no. 82. Pub. 361, Carnegie Inst. of Wash., p. 125.
(18) SABIN, F. R.: Bull. Johns Hopkins Hospital, 1921, xxxii, 314.
SABIN, DOAN AND CUNNINGHAM: Proc. Soc. Exper. Biol. & Med., 1924, xxi, 330.
(19) LEWIS, M. R.: Arch. exp. Zellforsch., 1925/26, ii, 228.
(20) HETHERINGTON AND PIERCE: Ibid., 1931, xii, 1.
(21) SABIN, F. R.: Amer. Rev. Tuberc., 1932, xxv, 153.
(22) GOTTLIEB, R.: Ibid., 1932, xxv, 172.
(23) MEDLAR, E. M.: Amer. Jour. Pathol., 1926, ii, 275.
(24) MEDLAR, E. M., AND KASTLIN, G. J.: Amer. Rev. Tuberc., 1927, xvi, 706.

THE SENSITIZATION OF GUINEA PIGS AND THE PRODUCTION OF ALLERGY AND ANAPHYLAXIS TO TUBERCULOPROTEIN[1,2]

H. S. REICHLE AND HARRY GOLDBLATT

In the course of investigations into the mechanism of the tuberculin reaction, an attempt was made to obtain the primary toxic substance predicated by Nicolle and considered by him to result from the digestion of tuberculin *in vivo*. Upon the hypothetical existence of such a substance is based the work of Bail, McJunkin, and others. However, its existence has not been unequivocally proved.

EXPERIMENTAL

On the assumption that the rapid diffusion of the primary toxic substance might render it difficult to obtain an appreciable quantity of it, the posterior chamber of the eye of a tuberculous guinea pig was chosen as a convenient site of injection of tuberculin in the hope that from this location the diffusion and adsorption would be less than from other sites, and the opportunity for the formation of the hypothetical toxic substance greater. This injection produced an extensive inflammation of the eye of the tuberculous animals, as was to be expected. These animals were killed after 24 hours, and 0.1 cc. of their eye-fluid injected intracutaneously into nontuberculous normal animals. In addition, 0.1 to 0.2 cc. of 1:10 tuberculin (O. T.) was injected intracutaneously in another area. No reactions occurred at the site of either of the injections. However, a very interesting phenomenon was observed which will be discussed at length in this paper.

When the injected animals were retested with tuberculin (intracutaneous application of O. T., 1:10) 72 to 96 hours after the first injections of O. T., and eye-fluid (referred to hereafter as *E. fl.*), a reaction occurred

[1] From the Babies and Childrens Hospital, Cleveland, Ohio, and from the Department of Pediatrics and the Institute of Pathology of the School of Medicine of Western Reserve University. Aided in part by a grant from the S. M. A. Current Fund, Babies and Childrens Hospital, Cleveland, Ohio, and from The Littauer Foundation, New York.

[2] Presented at the annual meeting of the American Association of Pathologists and Bacteriologists, April 29, 1932.

within 24 hours. Subsequent daily intracutaneous tests showed an increase in the degree of reactivity up to the 5th or 7th day. A photograph of guinea pig 597 (white, weight 900 gm., experiment E), figure 1, taken 7 days after the primary injections and 2 days after the last testing injection of O. T., illustrates that these reactions were classical "late reactions" (Zinsser (1)) of the bacterial-allergy type.[3] They were sharply circumscribed, firmly indurated, deep red, and often had a central area of paling. Their duration and development are shown in table 1. The reactions showed their climax in 24 to 48 hours after the test injection (see table 1). In the case of guinea pig 17 (174 gm., experiment D) the test injection made on the fourth day of the experiment kept increasing in

TABLE 1

Guinea-pig number 17 (given a sensitizing injection of E. fl. (eye-fluid) & O. T.)

NUMBER OF DAYS FOLLOWING THE SENSITIZING INJECTION: PRESENCE OR ABSENCE OF SKIN REACTION							
1 day	2 days	3 days	4 days	5 days	6 days	7 days	8 days
0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0
	−	−	II	+ (18 mm.)	+ (19 mm.)	+ (27.5 mm.)	+ (30 mm.)

The order of the testing injection for sensitization is indicated by a roman numeral.
0 = No skin reaction.
+ = Positive skin reaction.
− = No testing injection for sensitization given on that day.

size for a period of four days, but this was exceptional. The exact figures were 18 mm. at 24 hours, 19 mm. at 48 hours, 27.5 mm. at 72 hours, and 30 mm. at 96 hours. Though central paling was not uncommon, and evidence of slight central necrosis was present in several guinea pigs, in no case did vesicle-formation and ulceration take place. An indurated papule was often present after 10 days, and the return of the hair was delayed. Another characteristic of the classical tuberculin reaction is its ability to flare up anew on the application of tuberculin at some remote portion of the body (*Aufflammungsreaktion*). This was observed in the case of several reactions which were ten days old.

These reactions are highly suggestive of bacterial allergy. However, the absence of vesiculation and ulceration and the fact that the reactions

[3] In this study the two chief criteria used for allergy are a skin reaction of the type described above and the Long testicular reaction (see page 298).

usually reached their highest point of development at 24 hours are possible objections to this conclusion. The most critical test for a flare-up (*Aufflammungsreaktion*) is its demonstration in a reaction three to four

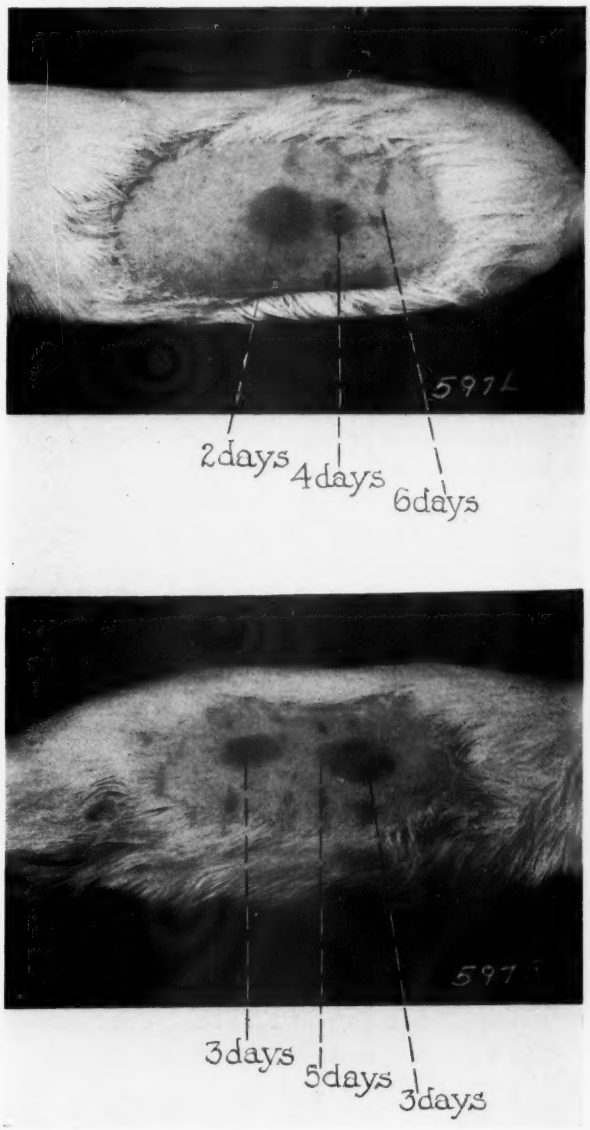


FIG. 1. Guinea Pig 597 sensitized with 0.1 cc. of O.T. 1:10. Reacting injections: 0.1 cc. of O. T. 1:10. Illustration of reactions from 2 to 6 days' duration.

weeks old. In this study the latest time at which such a reaction was observed was 10 days. Fernbach (2) (3) has laid great stress upon the last two points, and so has brought clarity into a field which was previously obscured by much uncritical work. Though the above criteria are important evidence of allergy, yet their absence does not necessarily exclude this condition. Tuberculin reactions of the 24-hour-acme type frequently have been observed in animals undoubtedly tuberculous. It is therefore probable that the differences observed between the reactions here described and those of highest degree of allergy are merely quantitative.

Four questions will immediately occur to students of tuberculin sensitivity:

1: Is this reaction an expression of sensitivity to tuberculoprotein?

2: Is it brought about by anaphylaxis?

3: Is it brought about by allergy?

4: Is it conditioned by allergy and anaphylaxis?

1: Old Tuberculin (O. T.) is a mixture of the constituents of the tubercle bacillus and of its culture medium. Long has frequently insisted that confusion must result from the use of a substance of so many components, and Fernbach (6) has shown how easily an individual injected with O. T. becomes sensitized to the glycerin-broth. Control tests were therefore carried out with the latter substance (own preparation and that of Parke, Davis & Company). At first, and at a time when the animals were already sensitive to O. T. and synthetic-medium tuberculin (S. M. T.), tests with glycerin-broth were negative, but upon repeated injections with O. T. the animals became sensitive to glycerin-broth also. However, it would not have been possible to eliminate the many other antigens furnished by the tubercle bacillus had not Dr. Florence Seibert graciously given us large quantities of her synthetic-medium tuberculin (S. M. T.) and her pure total protein tuberculin (T. P. T.) (4). To both of these substances the animals reacted in exactly the same fashion as to Old Tuberculin (O. T.). It is of further interest and particularly important as evidence for the specificity of the sensitivity that they also reacted to watery extract of tubercle bacillus kindly furnished us by Dr. H. S. Willis.

This proves the existence of a sensitivity to tuberculoprotein. It is obvious that by the use of large amounts of O. T. a sensitivity to some of the bouillon constituents might be induced and that this, in the absence

of a pure product such as that of Seibert, might overshadow the tuberculoprotein sensitivity itself. However, another possibility must be mentioned,—that of a heterogenic relationship between some constituent of some lots of glycerin-broth and tuberculoprotein itself. Suggestive evidence of such a condition has come from many workers. Moro and Keller (5) reported on a lot of glycerin-broth from the Hoechst Laboratories which gave apparently as specific and typical reactions as O. T. itself, while other lots from the same firm gave no reactions. One of us (R.) several years ago tested the same lot of glycerin-broth with which Moro and Keller obtained positive reactions, and obtained a positive result. However, Fernbach (6) pointed out that the possibility of contamination with O. T. in the process of manufacture was not excluded. P. D'Arcy Hart (7) has reported on several hundred skin reactions with a lot of glycerin-broth which gave reactions analogous to those of O. T. Rich (8), in the course of experiments to desensitize tuberculous guinea pigs, found that the animals treated with glycerin-broth were desensitized for O. T. In the present study a reaction to glycerin-broth (Parke, Davis) was observed in one guinea pig which was sensitized to T. P. T. by T. P. T. alone. There is at least a theoretical basis for a possible heterogenic relationship between glycerin-broth and O. T. in the recent work of Seibert. She has shown that the original molecule of tuberculoprotein may gradually be broken down and that the fractions retain antigenic power down through several manipulations. The fraction in O. T. is probably one of the last potent fractions, for a mere precipitation with trichloracetic acid is sufficient to destroy its value as an antigen. Is it therefore not possible that, in some lots of glycerin-broth, fractions may be found corresponding in chemical nature with fractions found in the denatured O. T.?

Moro and Keller (9), in 1925, reported that they were able to obtain allergic reactions to O. T. by sensitization with smallpox vaccine and O. T. Many workers have described reactions of a similar nature (10). Some have considered them expressions of an anaphylactic sensitivity, while others have been inclined to regard them as truly allergic. In the present study, atypical reactions to O. T. obtained in animals that had been injected repeatedly with O. T. drew our attention at first in the direction of anaphylaxis.

2: By means of the Dale test anaphylactic sensitivity of the guinea pig uterus to O. T. and to S. M. T. was investigated. The experiments

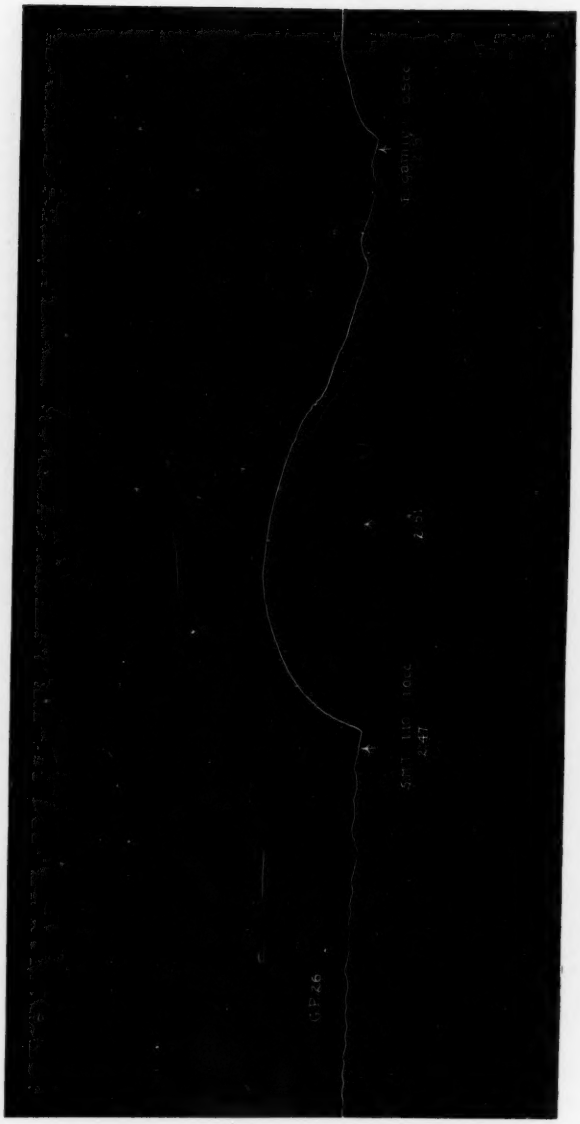


FIG. 2. Dale test. G. P. 26 (Exp. K). Sensitized with E. fl. + O. T. Ergamine used was a solution of Burroughs Wellcome ergamine-acid-phosphate, of which 1 cc. = 0.0001 gm.

were carried out according to the technique described by Dale in the English *System of Bacteriology* (11). The capacity of the bath was 250 cc. The largest amount of S. M. T. or O. T. used was 1 cc. (1:10). Old Tuberculin of this strength caused slight contractions of a very

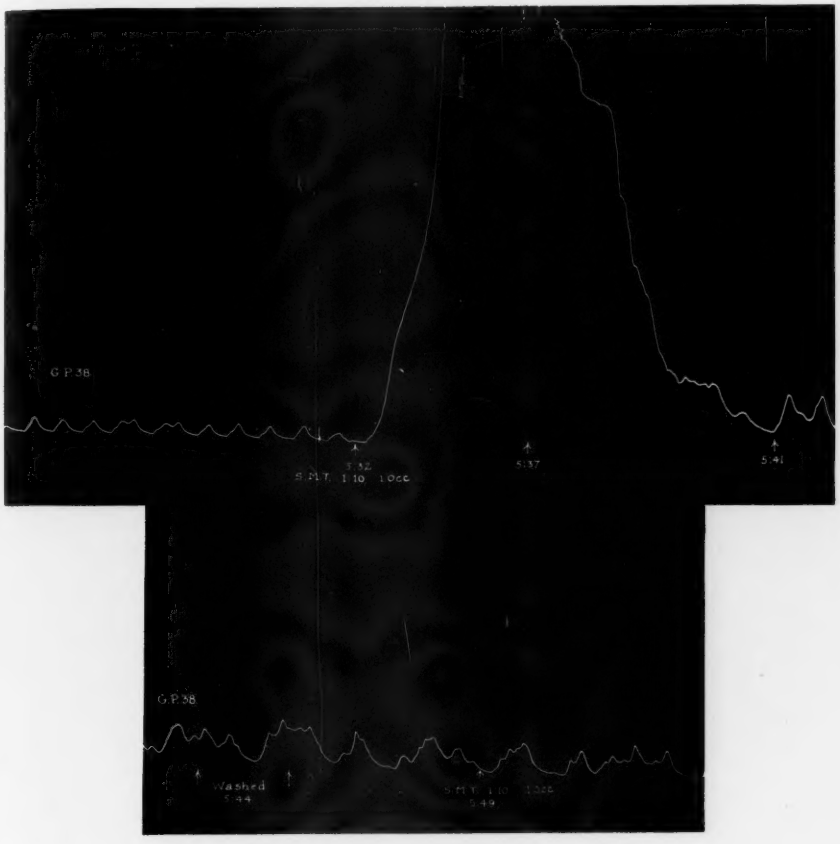


FIG. 3. Dale test. G. P. 38 (Exp. A4). Sensitized with E. fl. T. P. T. (Seibert). After reaction to S. M. T. (upper part of fig. 3) and washing of uterus, the organ did not respond to the same dose of S. M. T. (desensitization phenomenon). However, the uterus responded subsequently to 0.5 cc. and 1.0 cc. of a solution of ergamine-acid-phosphate (0.003 gm. ergamine-acid-phosphate in 100 cc. of Locke's solution).

active uterus of a normal animal, but S. M. T., even in a dose of 2 cc. (1:10), had no appreciable effect. The contractions, obtained in animals sensitized to O. T. or other tuberculin products, compared favorably with those obtained by watery extract of tubercle bacilli in animals sensitized to this substance. (See figures 2 and 3.)

3: Many tests for allergy have been proposed, such as the Koch-Roemer reinfection, the Patterson pleural phenomenon, the Pfeiffer peritoneal phenomenon, and the Long testicular reaction. In this study, the Long test (12) was chosen because it is apparently a purely allergic phenomenon without the implication of resistance involved in

TABLE 2

Testicular Tests (Long)

	SENSITIZING TREATMENT	SKIN REACTION	TESTICULAR INJECTION	RESULT AT 36 HOURS	RESULT AT 3 WEEKS
A_{10} 82	TPT. E fl.	±	TPT.	0	0
A_{10} 372	TPT. E fl.	+	TPT.	0	0
P 70	OT. E. fl.	2+	OT.	+	+ Tested with TPT. & WE.
A_5 906	TPT. E fl.	0	OT. A	0	
A_5 903	TPT. E fl.	0	OT.	0	
A_5 901	TPT. E fl.	+	OT.	0	
A_5 902	TPT. E fl.	0	OT.	0	0
W 394	Horse-serum OT. *	0	H. S.	0	0
F 25	OT. E fl.	0	SMT.	0	0
F 27	OT. E fl.	0	SMT.	0	0
L 64	OT. E fl.	0	SMT.	0	0
O 94	OT. E fl.	±	SMT.	0	0
E 597	OT. E fl.	2+	OT.	±	+
V 156	OT. E fl.	±	OT.	0	0
T 398	OT. E fl.	±	OT.	0	0
A^{12} 71	OT.	+	SMT.	0	
A^{12} 75	E fl. OT.	2+	SMT.	+	+
A^{12} 73	E fl. OT.	2+	SMT.	+	+
A^{13} 14	OT.	+	TPT.	±	
A^{13} 390	OT.	+	TPT.	±	

* Strongly skin positive to horse-serum.

Skin reactions (column 3) are in response to the same tuberculin product used as sensitizer (column 2).

the other tests. It is also much more sensitive, a fact of great importance in experiments such as these, in which the animals are not likely to show a high degree of allergy. Table 2 summarizes the results of the Long test on 20 guinea pigs. Most of these animals received an injection of 0.1 cc. of 1:10 O. T. or S. M. T. or T. P. T. into each testis. The right testis was removed at 36 hours, the left at 3 weeks. The histological technique consisted of immediate fixation in 10 per cent formalin, embedding in

paraffin, and staining with haemotoxylin-eosin. Only such specimens were regarded as positive which at 36 hours showed degeneration and necrosis of the germinal epithelium, with complete disappearance of spermatozoa, and an extensive infiltration of the intertubular spaces with an inflammatory exudate consisting of fluid, fibrin (reticulum?) and mononuclear cells (see figure 4). At 3 weeks a positive reaction in the other testis still showed some intertubular exudate in some of the animals. However, this was in great measure organized and partially replaced by

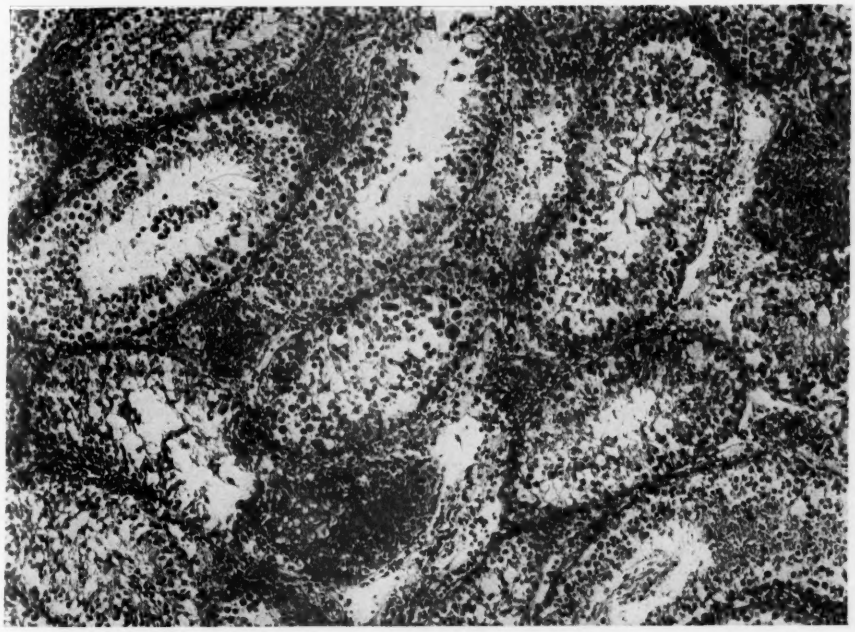


FIG. 4. Long test. 36-hour reaction. H. & E. stain. × 120. Guinea Pig 70. Experiment P. (See table 2.)

a proliferation of the interstitial cells of Leydig. The tubules by this time had lost almost all of their germinal cells and showed in general only a basement membrane, or at most only a poorly preserved spermatogenic layer (figure 5).

Only those animals which had shown a strongly positive prolonged skin test of the allergic type developed a positive Long testicular test. Animals with weaker skin reactions had either negative or questionable Long tests. Animals which had developed fugitive skin reactions of the anaphylactic type (see below) were uniformly negative. If, therefore,

the Long test is indicative of an allergic state exclusively and if it does not respond to an anaphylactic mechanism, as appears probable from the work of Long and Seyfarth (13), as well as from our experience with guinea pig W-394 (table 2), then allergy to tuberculoprotein has been demonstrated in some of the animals in this study. The correlation of the prolonged skin reaction with the positive testicular test is also suggestive.

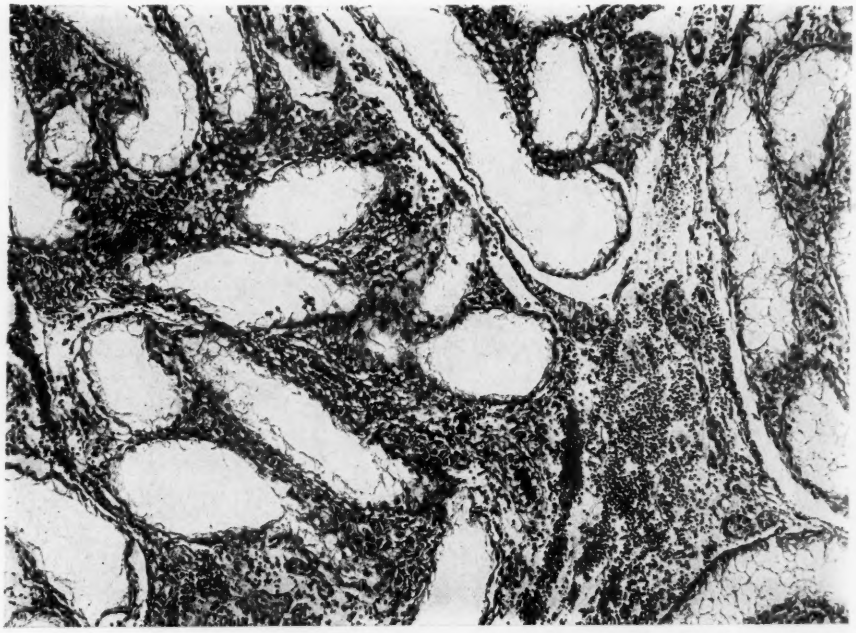


FIG. 5. Long test. After three weeks. H. & E. stain. × 120. Guinea Pig 70. Experiment P. (See table 2.)

4: It appears therefore that an allergic and an anaphylactic mechanism is involved in the reaction. Whether these are present together in the same guinea pig at the same time cannot be stated because the allergic manifestation was observed in males and the test for anaphylaxis was carried out on females. Of 102 pigs only 55 developed skin reactions of the allergic type. Many of the remainder developed the anaphylactic type of skin reaction. This type is illustrated by guinea pig 1788 (white male, experiment L, 425 gm.), which reacted to the fifth injection of O. T. with a red induration which measured 30 mm. at 24 hours. There was a central blue area of 7 mm. At 48 hours, however, only an area of deep

induration remained and at 72 hours all trace of reaction was gone. The skin test with glycerin-broth (own lot) was negative. This type of reaction is less sharply defined than that of bacterial allergy, it may show concentric rings of redness and pallor, and the edges are suggestive of pseudopodia. We have found that animals showing a typical allergic skin reaction develop the anaphylactic type of skin sensitivity if they are repeatedly injected with O. T. They may even become entirely insensitive. During the period of anaphylactic skin reactivity, the animals do not show a positive Long test. That this is not merely a sensitivity to glycerin-broth is shown by the fact that they react in exactly the same fashion to both T. P. T. and W. E. Hence there appears to be little doubt that the guinea pig may react to the same substance (tuberculoprotein) by these apparently different mechanisms, an observation which offers substantial support to the theory that allergy and anaphylaxis are closely related phenomena. The exact nature of this relation remains unknown. It has been suggested that the early injections sensitize the cells of the body, so producing the allergic state, and that on subsequent injection, antigen escapes into the blood, and induces the formation of an anaphylactic humoral antibody. It is known that the allergic state develops long before the anaphylactic in the experimental tuberculosis of the guinea pig. However, one of the animals which gave a very powerful uterine reaction to S. M. T. (38 A^4) (figure 3) had received only five injections of T. P. T. The Dale test was done 29 days after the first injection and 23 days after the last positive allergic skin reaction.

The presence of a definite incubation period appears to point to an antigen-antibody mechanism and permits a comparison of this reaction with the Arthus phenomenon. In all the cases shown in table 3, Old Tuberculin or tuberculoprotein, with or without an adjuvant, was injected on the first day of the experiment. The injections of O. T. or T. P. T. were repeated on subsequent days. Between the first injection and the appearance of the first reaction to a subsequent injection at least three and sometimes as many as 8 days intervened. After the sensitizing injection, the animals may be in a state susceptible to a reaction to a second injection for as long as 53 days. Further proof of the presence of an incubation period is seen in the fact that the injection, which had been given previous to the third or fifth day and had been negative at 24 or 48 hours, may suddenly flare up concomitant with a reaction of the last injection.

Since Bail's publication in 1910 (14), many workers have reported suc-

cessful sensitization with tuberculin. Table 4 summarizes in a very cursory fashion the work which has been published on this subject since 1921. Practically every worker has used some adjuvant substance because of the universal conviction that Old Tuberculin does not contain a complete antigen.[4] Landsteiner's theory of the haptene and his success in sensitizing animals to haptenes by the addition of a full antigen (the *Schleppersubstanz* of the Germans) has lent a substantial theoretical

TABLE 3

Summary of time relations in tuberculin sensitization

NUMBER OF ANIMALS	SENSITIZING INJECTION	NUMBER OF DAYS FOLLOWING SENSITIZING INJECTION												
		1	2	3	4	5	6	7	8	9	10	11	53	54
5	E. fl. & O. T.	I	II	III	IV	+								
13	E. fl. & O. T.	I	II	III	IV	V	+							
3	E. fl. & O. T.	I	0	0	II	+								
3	E. fl. & O. T.	0	0	0	I	II	+							
1	E. fl. & O. T.	0	0	0	0	I	0	II	+					
1	E. fl. & O. T.	0												+
4	E. fl. & T. P. T.	0	I	II	III	IV	+							
1	E. fl. & T. P. T.	0	0	I	II	+								
1	E. fl. & T. P. T.	0	0	I	+									
2	O. T.	0	0	0	I	+								

Roman numeral = the order of the testing injection for sensitization. The testing injection consisted of either O. T. or T. P. T., and always corresponded in type to the one used in the sensitizing injection.

E. fl. = Eye fluid.

0 = No skin reaction.

+ = Positive skin reaction.

foundation to this work. The results of the present study make it doubtful that the adjuvant substances used were necessary factors. Analogous reactions were obtained when O. T. was injected together with the eye-fluid of tuberculin-injected tuberculous guinea pigs, with the eye-fluid of normal guinea pigs, the eye-fluid of normal cows, and latterly with horse-serum. Finally several of the normal controls which were

[4] At the meeting of the American Association of Pathologists and Bacteriologists (April, 1932) Seibert announced that she had succeeded in demonstrating the presence of a protein in O. T.

injected with O. T. *alone* gave reactions to O. T. in no way different from those obtained when an adjuvant substance was injected with it. It would indeed be strange if a substance so poor in antigenic qualities as eye-fluid could act as a complete or even supplementary antigen. The fact that O. T. by itself was able to sensitize some of the animals minimizes the importance of the many adjuvant substances used by various workers, and indicates that the necessary factor in the phenomenon was the O. T. itself. In this way apparently conflicting claims become harmonized.

TABLE 4

Summary of literature on tuberculin sensitization

NAME OF AUTHOR	YEAR	TECHNIQUE	TEST OBJECT	FIRST REACTION
McJunkin	1921	Ascitic fl. tbc. pig	guinea pig	8–9 days
Moro-Keller	1925	Vaccine + O. T.	human	few weeks
Moro-Keller	1925	Pig serum + O. T.	human	few weeks
Yu	1925	Coli vaccine (+ O. T. ?)	?	8 days
Yu	1925	Normal g. p. organ (+ O. T.?)	?	?
Lange	1925	Coli vaccine + O. T.	guinea pig	4 weeks (?)
Hain	1925	Partigens + O. T.	?	?
Zinsser-Taniya	1926	Rabbit serum + O. T.	guinea pig	6–8 days
v. Groer	1926	Pig serum + O. T.	guinea pig	3–14 days
v. Groer	1926	Pig serum + O. T.	human	18 days
Adam	1926	"Sensibilizer" + O. T.	?	?
Nobel-Rosen	1926	Vaccine + O. T.	human	10 days
Keller-Doelter	1927	Serum protein + O. T.	?	?
Lehner-Rajka	1927	Repeated "depot" of O. T.	?	5 days
Haemel	1928	O. T. subcutan.	human	?

Why then have other workers failed to substantiate these results? An analysis of the present study indicates the importance of the consideration of the following factors. Undoubtedly the importance of the incubation period has been neglected in the past, although a glance at table 4 shows that almost all workers have observed it. The skin test is a very unsatisfactory measure of allergy because of its variability from animal to animal, the wide latitude it gives to subjective factors, and the fact that there are no sharp boundaries for end-readings. The Long testicular reaction is a much more satisfactory index of allergic sensitization, not only because of its greater objectivity and the permanent documentary evidence which it affords, but also because it apparently is free from nonspecific reactions

or border-line results. Great importance, furthermore, should be ascribed to our observation that the allergic state may be of very short duration (one or two weeks) if the animal receives repeated injections.

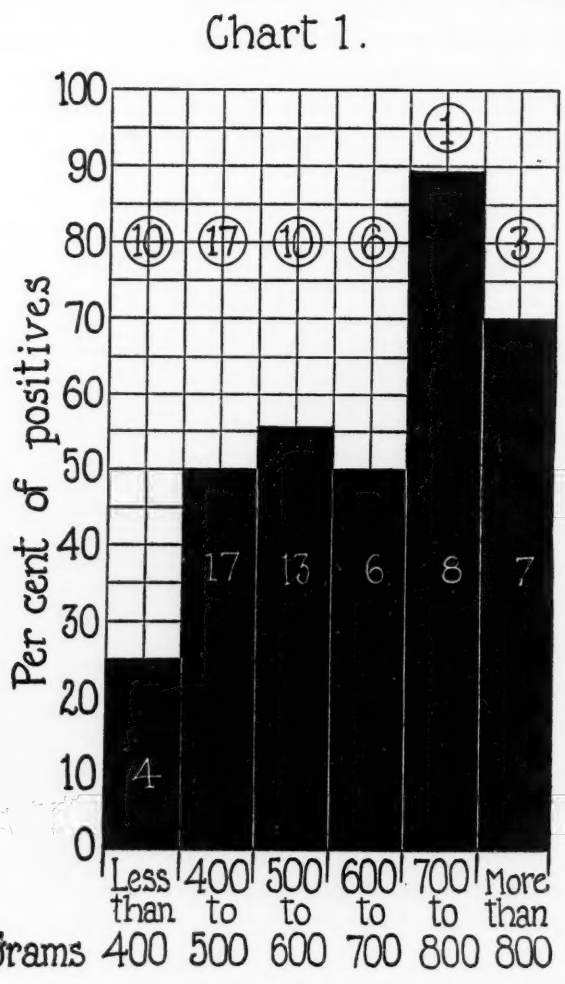


CHART 1. Illustrates the relation of body weight to the percentage of animals successfully sensitized. The numerals in the black columns give the number of animals sensitized in every group, and the numerals in the white columns indicate the number that showed no sensitization.

Hence the experimentalist may miss the allergic state in attempting to increase the degree of sensitivity. However, apparently the most important factor is the weight of the tested animals. Chart 1 shows

that in this study animals below 500 gm. were very poor reactors, and that a large percentage of reactors occurred in animals weighing more than 700 gm. It is well known that small young animals are refractory to any immunological stimulation. Petroff (15) was the first to observe this fact in the vaccination of guinea pigs with dead tubercle bacilli and Fernbach (16) verified his reports. Young animals are inconstant in their precipitin and agglutinin titre. Guinea pigs under one month of age may fail to give a positive tuberculin reaction even when infected with the tubercle bacillus. Freund (17) has published several reports on this subject, as have also Famulener (18) and Kligler and Olitski (19). Even heavy animals may fail to be sensitized to tuberculin substances if they are not in a perfect state of health. Here also can be pointed out the parallelism to the experience of both Fernbach and Petroff. Hence, it does not seem improbable that the negative results obtained by many workers may be ascribed to one or more of the factors enumerated above.[5]

One important difference between the artificial allergic sensitization produced with O. T. and that seen in tuberculous infection is to be found in the fact that animals artificially sensitized are very easily desensitized. There appears to be a limit of rather low sensitivity determined by individual susceptibility beyond which it is impossible to go. Further injections, instead of resulting in increasing the allergic state as is so characteristic for the tuberculous animal, serve only to decrease it. As stated above, enough is not known about the time relations between the development of the allergic and anaphylactic states in these experiments; hence it is not possible to say that the allergic passes over into an anaphylactic phase. Both are certainly examples of cellular and not of humoral reactions (Rich (20), Weil (21)).

CONCLUSIONS

Normal guinea pigs were injected intracutaneously with 1 to 10 Old Tuberculin and various adjuvant substances, such as eye-fluid of normal guinea pigs and horse-serum. Upon retesting these animals with Old Tuberculin 3 to 8 days after the sensitizing injection, the animals responded in a fashion typical of bacterial allergy. Fifty-five of 102 animals used in these experiments have shown this phenomenon.

The skin reactions were of the prolonged, allergic type, and, although vesiculation and ulceration were never seen, they were otherwise analo-

[5] In a personal communication Arnold Rice Rich has suggested that the intracutaneous administration may have been a factor of considerable importance.

gous to those observed in tuberculous animals. The same reaction was obtained with Seibert's pure tuberculoprotein. At an early stage of an experiment the animals were not sensitive to glycerin-bouillon, but after repeated injections with Old Tuberculin they developed sensitivity to the glycerin-broth. In some of the animals a positive Long testicular test for allergy to tuberculin was obtained; in others a strong anaphylactic sensitivity to tuberculin was demonstrated by means of the Dale test.

It is probable that an adjuvant substance is not a necessary factor and that the essential element in all previous reports of successful artificial sensitization to tuberculin has been the tuberculin itself. Some of the reasons why others have not been able to substantiate these claims are probably the failure to recognize the incubation period, the use of animals weighing less than 500 gm. that are not easily sensitized, and the lack at that time of an objective measure of allergy, such as the Long testicular test.

We express our thanks to Frederick Beal, member of the technical staff of the Babies and Childrens Hospital, for faithful and intelligent technical assistance.

REFERENCES

(1) ZINSSER, H.: Studies on the tuberculin reaction and on specific hypersensitiveness in bacterial infection, J. Exper. Med., 1921, xxxiv, 495.

(2) FERNBACH, H.: Cutaneous tuberculin allergy after intracutaneous simultaneous inoculation of tuberculin and vaccinia virus; comment on Moro and Keller's article, Deutsche med. Wchnschr., 1925, li, 1983.

(3) FERNBACH, H.: Specificity of tuberculous focal reactions and state of nonsensitivity which follows general reactions, Beitr. z. Klin. d. Tuberk., 1926, lxiii, 60.

(4) SEIBERT, FLORENCE B., AND MUNDAY, BETTY: The chemical composition of the active principle of tuberculin, Amer. Rev. Tuberc., 1931, xxiii, 23.

(5) MORO, E.: Allergy and parallergy, Monatschr. f. Kinderhk., 1926, xxxiv, 193.

(6) FERNBACH, H., AND HERZGER, G.: Tuberculin and bouillon sensitivity, Beitr. z. Klin. d. Tuberk., 1927, lxvii, 666.

(7) HART, P. D'A.: The specificity of skin reactions in man in relation to tuberculous infection, Quart. J. Med., 1932, n.s. i, 49.

(8) RICH, A. R.: Personal communication.

(9) MORO, E., AND KELLER, W.: Tuberculous skin allergy following simultaneous injection of tuberculin and smallpox vaccine, Deutsche med. Wchnschr., 1925, li, 1015.

(10) NOBEL, E., AND ROSENBLÜTH, A.: A contribution to the study of tuberculin and protein sensitivity of the skin, Ztschr. f. Kinderhk., 1925, xxxix, 439.

NOBEL AND ROSEN: The non-specific skin reactions produced by simultaneous inoculation with vaccine and protein substances, Gesellschaft f. inn. Med. u. Kinderhk., Pädiatrische Sektion, Wien, 1925. (Abstr. Klin. Wchnschr., 1926, v, 630.)

KELLER, F.: Attempts to sensitize guinea pigs to old tuberculin by non-specific methods, Ztschr. f. Hyg. u. Infektionskr., 1927–28, cviii, 784.

v. GRÖER, F., AND MATERNOWSKA, Z.: Studies in tuberculin activity, Monatschr. f. Kinderhk., 1929, xliv, 141.

(11) DALE, H. H.: The use of isolated plain muscle in testing for anaphylaxis, A System of Bacteriology, London, 1931, ix, 229.

(12) LONG, E. R.: Standardization of tuberculin, J. Infect. Dis., 1925, xxxvii, 368.

(13) LONG, E. R., AND SEYFARTH, M.: The testicle as an indicator of allergy in the hypersensitiveness of infection and anaphylaxis, Amer. Rev. Tuberc., 1924, ix, 254.

(14) BAIL, O.: The transfer of tuberculin sensitivity, Ztschr. f. Immunitätsforsch. u. exper. Therap., 1910 (orig.), iv, 470.

Further experiments on the passive transfer of tuberculin sensitivity, Ibid., 1912 (orig.), xii, 451.

(15) PETROFF, S. A.: Immunological studies in tuberculosis, II, J. Immunol., 1924, ix, 309.

(16) FERNBACH, H.: The production of local tuberculin sensitivity in guinea pigs and humans (an examination into the method of simultaneous inoculation with tuberculin and vaccine proposed by Moro and Keller), Beitr. z. Klin. d. Tuberk., 1926, lxiv, 660.

(17) FREUND, J.: The sensitiveness of tuberculous guinea pigs one month old to the toxicity of tuberculin, J. Immunol., 1929, xvii, 465.

Influence of age upon antibody formation, Ibid., 1930, xviii, 315.

(18) FAMULENER, L. W.: On the transmission of immunity from mother to offspring; a study upon serum hemolysins in goats, J. Infect. Dis., 1912, x, 332.

(19) KLIGLER, I. J., AND OLITZKI, L.: Antibody production by young and mature animals, Ztschr. f. Hyg. u. Infektionskr., 1929, cx, 459.

(20) RICH, A. R., AND LEWIS, MARGARET R.: The nature of allergy in tuberculosis as revealed by tissue culture studies, Bull. Johns Hopkins Hosp., 1932, l, 115.

(21) WEIL, R.: Quoted in Chemical Pathology, H. Gideon Wells, Philadelphia, ed. 5, 1925, p. 224.

A TAPE TEST WITH TUBERCULIN OINTMENT[1]

ERNST WOLFF

with the assistance of

MAX H. TEITLER

In the last ten years, various tuberculin ointments without controls have been used in Europe for diagnostic purposes. These are directly applied to the skin by rubbing, and have been found quite satisfactory in ease of application, stability of the preparation, and sensitiveness of reaction as compared to the intracutaneous test. As no American preparation was available, I have devised a tuberculin ointment and ointment control which have been prepared for me for experimental purposes. The ointment contains a highly concentrated tuberculin and killed tubercle bacilli incorporated in an ointment base which is able to penetrate into the *cutis*. The ointment control contains every constituent of the tuberculin ointment, with the exception of the tuberculin and the tubercle bacilli.

Technique: The area of application is the paravertebral region between the eighth and eleventh thoracic vertebrae. The skin is cleansed with green soap and water, dried gently, bathed with benzene, and then gently dried again. A pea-sized drop of the semiliquid tuberculin ointment is applied on the right side, and a similar-sized drop of the control ointment on the left side. Each of these drops is covered tightly with a two-inch square of adhesive tape.

Reading: The test is read in forty-eight hours. Adhesive tape is removed after soaking with benzene and the area gently cleansed with benzene. Ten minutes after removal, the reaction may be clearly observed.

A positive reaction exhibits papules, erythema, induration and pigmentation. A weakly positive test shows a few, up to 20 discrete papules, 1 to 3 mm. in diameter, each of a pale rose color. A medium reaction shows very many vividly red papules, with erythema of the skin sur-

[1]From the Pediatrics Departments of the University of California Medical School and the Mount Zion Hospital, San Francisco, California.

rounding them. A strong reaction shows, in addition, changes of the entire test area, consisting of yellow-brown pigmentation, indurated plateau formation, and marked reddening. A few, up to all of the papules, may even show vesiculation. The yellow pigmentation of the entire test area is easily demonstrated by stretching the skin.

In weak reactions it is advisable to palpate the area in order to detect the follicles.

Course of reaction: The peak of the reaction is reached after seventy-two hours. The color begins to fade in ninety-six hours, but is still faintly discernible in one week. Medium reactions show a definite scaling up to approximately ten days, and, in the marked reaction, even after two weeks there may still be roughening of the skin, brownish discoloration, and infiltration and scaling of the area. In contradistinction to the intracutaneous test, there has never, so far, been a generalized systemic reaction, such as rise in temperature, malaise, or focal signs. Subjective symptoms accompanying the local reaction are mild. In nearly every positive case there is some itching over the test area, with only slight discomfort.

Results: Three groups of patients were tested:

1: Fifty-nine clinically tuberculous children were tested simultaneously with the ointment and with intracutaneous injections of 0.1 cc. of Old Tuberculin, human, 1:1000. If the intracutaneous test was negative, the patient was retested with 0.1 cc. of O. T. of 1:100 and 1:10 concentration.

2: Forty-three children of the Yuma Indian Reservation were tested by Dr. J. Lloyd Eaton of Oakland, California, simultaneously with Tuberculin Ointment and O. T. 1:1000. In this group it was shown that the ointment test as a routine procedure may give valuable results in the hands of a physician who is not familiar with the technique of this new test.

3: Eighty-eight cases of the Children's Chest Clinics of the University of California and Mount Zion Hospital were tested simultaneously with the ointment and intracutaneous tuberculin injections, dilution 1:100. In cases of disagreement, the patients were retested with tuberculin 1:10.

Agreements between ointment test and intracutaneous test: The sum-total of tested cases was 190. Both tests, considering all dilutions, were positive in 120 cases and both negative in 62 cases, making a total agreement of 182 cases, or 95.8 per cent of all three groups combined. The percentage of agreement in the first two groups combined was 97 cases,

or 95 per cent. The 88 cases of the third group showed a total agreement in 85 patients, or 96 per cent.

Discrepancies: In all three groups combined, 8 cases, or 4.2 per cent, showed disagreement. In 5 cases with negative ointment tests and positive intracutaneous tests, one showed a positive intracutaneous only with a dilution of 1:10. Two cases were positive with human O. T., dilution 1:100, and 2 cases with human O. T., dilution 1:1,000. In the last 2 cases, at least, there was roentgenological evidence of a tuberculous infection. In the 3 cases, in which the ointment test was positive and all dilutions of the intracutaneous test were negative, one was diagnosed clinically as bone tuberculosis. In 2 cases no clinical evidence of tuberculosis was found.

Sensitivity: The high percentage of agreement shows in general the sensitiveness of the ointment test. In 3 cases the ointment test was positive and the intracutaneous tests of 1:100 were positive, whereas the dilution 1:1,000 failed to produce a positive reaction. In one case the dilutions 1:1000 and 1:100 were negative, and only the dilution 1:10 corroborated the positive result of the ointment test.

It is thus fair to assume that the degree of reaction to the ointment test is generally comparable with the degree of reaction produced by the intracutaneous test, using a tuberculin dilution 1:100.

SUMMARY AND CONCLUSIONS

1. The technique of application and reading of a tuberculin-ointment tape test, with control, is described.

2. The ointment is easier to apply, and causes less psychic disturbance and less untoward reactions than does O. T. in the intracutaneous method of testing.

3. The agreement between the ointment test and the intracutaneous test in all dilutions, as applied to 190 children, was 95.8 per cent.

4. The ointment test is generally comparable in results with the intracutaneous O. T. test in a dilution of 1:100.

A METHOD OF RECORDING ROENTGEN-RAY READINGS

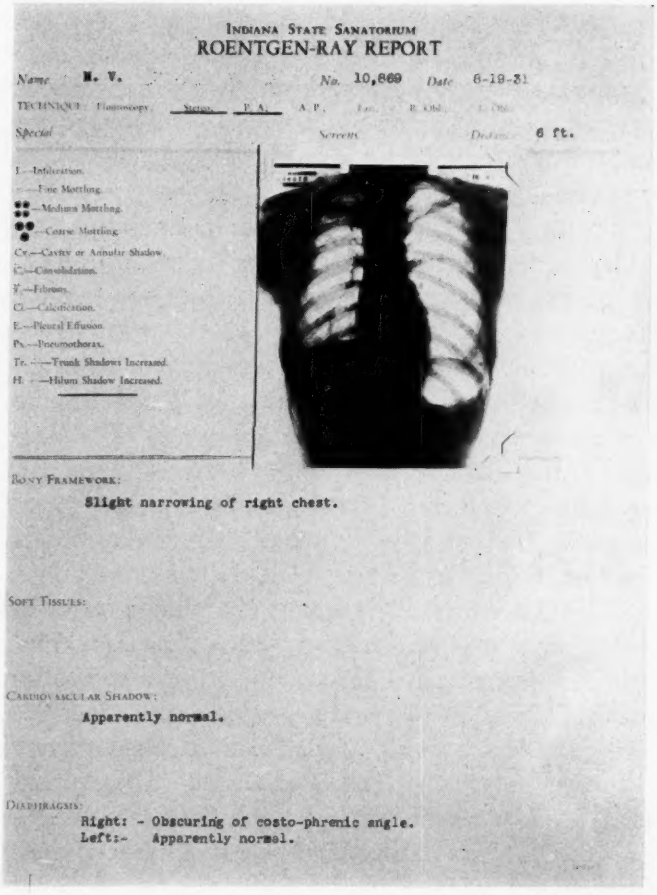
H. B. PIRKLE[1]

For the past three years we have been using a method of recording readings of chest roentgenograms which makes use of photographic copies of films, and which we have found to be of practical value in institutional work. It has also proved of value in our outpatient department when it is necessary to send the attending physician a transcript of the X-ray reading. A small photographic copy of the film is attached to the sheet on which the reading is recorded, thereby facilitating the comparison of serial films and making available an exact, though greatly reduced copy of the roentgenogram, rather than a diagrammatic or written record alone. The method also has the advantage of low cost and requires a relatively small expenditure of time.

We use a printed record blank as shown in the accompanying figures, printed on both sides and with a blank space on the front, where the copy of the roentgenogram is attached by the use of mounting corners such as are used for mounting kodak pictures. In preparing the prints, the film to be copied is placed on the illuminator and photographed directly on Press bromide paper with an Eastman clinical camera, no photographic films or plates being required in the process. With the strength of illumination and distance we use, an average exposure of 20 seconds is required with the lens opening at F. 16. Variations of these factors would, of course, change the time of exposure. The exposed paper is then developed and fixed in the X-ray solutions, no special developer being required. The developing time is about three minutes. After fixing, the prints are washed in the usual manner and soaked for a few seconds in a 5 per cent glycerin solution to prevent excessive curling of the prints on drying.

While we copy only one film at a time it would be possible by using multiple illuminators and a larger camera to copy several at a time if care were taken to select films of approximately equal density for each exposure. After drying, the prints are mounted on the record sheets in

[1] Indiana State Sanatorium, Rockville, Indiana.



INDIANA STATE SANATORIUM
ROENTGEN-RAY REPORT

Name **H. V.** *No.* 10,869 *Date* 6-19-31

TECHNIQUE: Fluoroscopy ____ Stereo. ____ P. A. ____ A. P. ____ Lat. ____ R. Obl. ____ L. Obl. ____

Special ____ *Screens* ____ *Distance* 6 ft.

I.—Infiltration.
.—Fine Mottling.
—Medium Mottling.
—Coarse Mottling.
Cv.—Cavity or Annular Shadow.
C.—Consolidation.
F.—Fibrosis.
Cl.—Calcification.
E.—Pleural Effusion.
Px.—Pneumothorax.
Tr. ↑—Trunk Shadows Increased.
H. ↑—Hilum Shadow Increased.

BONY FRAMEWORK:
Slight narrowing of right chest.

SOFT TISSUES:

CARDIOVASCULAR SHADOW:
Apparently normal.

DIAPHRAGMS:
Right: - Obscuring of costo-phrenic angle.
Left:- Apparently normal.

FIG. 1

TRACHEA AND MEDIASTINUM:
Trachea displaced slightly to right.

PLEURA:

LUNG FIELDS:
HILUM:
Apparently normal.

TRUNK SHADOWS:
Some increased density of trunk markings in right base.

LUNG FIELDS PROPER:

Right:- Moderately coarse mottling throughout, more marked above 3 r. 7 v.s. There is a moderately thick-walled annular shadow 3 x 2 cm. in size at level of clavicle in midole lung zone. Shadows are moderately soft.

Left:- Rather indistinctly outlined density about 1½ cm. in size at level of 4 r. 9 v.s. in middle lung zone. There is a small calcification about 3/4 cm. in diameter just above lateral portion of diaphragm.

CONCLUSIONS:
Pulmonary Tuberculosis, Moderately Advanced. Cavitation upper right. Probably moderately active.

FORMULA: _____

Read by _____

FIG. 2

the manner mentioned above and allowed to press for a few hours, after which they are filed in the patient's clinical record. We have used this method only in chest work but there is no reason why it is not applicable to the recording of any kind of roentgenograms.

Figure 1 shows the printed sheet with the photograph mounted thereon, and figure 2 the reverse side of this same sheet.

SUMMARY

A method is described for recording roentgen-ray readings, which makes use of a reduced copy of the film, photographed directly on Press bromide paper and processed with X-ray solutions, this copy being mounted with the written report. The advantages are the ease with which serial films can be compared, low cost, and relatively small expenditure of time.

THE RÔLE OF EMOTION IN TUBERCULOSIS[1]

MARY B. EYRE[2]

In dealing with the effect of emotion on an organism which is at the same time reacting in its own defense against the ravages of the tubercle bacillus, let us cast away generalizations and classifications, behind which it is so easy to hide, and drive straight to the simplest aspect of the facts before us.

Let us think, then, of the human organism as a unitary whole, trying to get along according to the laws of its entire being. Thus conceived, we need not separate mind and body, much less "soul" and "body;" but regard the individual as making responses to his environment, both internal and external, with the use of all of his functions, his endowment, his learning and experience.

The human being, because of his more complex nervous system and bigger brain, is better able to make new responses with respect to shiftings of his environment than are the lower animals, which are more rigidly controlled by their inherited behavior patterns which we call "instincts" or "instinctive tendencies." Man can remember, plan, and, within limits, choose his course with insight derived from past experience; and modern neurologists and physiologists (Sherrington, Herrick, Child, Cannon, *et al.*) teach us that the development of the nervous system depends chiefly on *use*, from the striving which arises from within the organism itself.

Man, being animal plus, retains his animal feelings, along with his improvable brain to control the direction and output of energy.

The growth energy of the human organism, which can develop a seven-pound infant from a fertilized ovum weighing at conception six ten-thousandths of a gram, in nine calendar months, does not cease with the end of somatic growth, but flows through all conscious and unconscious manifestations of the individual life, while life lasts.

This energy, primarily a growth function, is inherent in the stirred-up

[1] Read at a session of the Clinical Section at the twenty-eighth annual meeting of the National Tuberculosis Association, Colorado Springs, Colorado, June 7, 1932.

[2] Department of Psychology, Scripps and Claremont Colleges, Claremont, California.

feeling which we call *Emotion*. The derivation of the word,—*E*, out of, and *moveo*, I move, shows that implicit in emotion is movement—action —energy. Emotion means therefore potential energy, which becomes kinetic through gland and muscle. Something is coming out.

It is a law of physiology that energy, which manifests through the nervous system as nervous impulse, must discharge eventually in muscle, gland, or another nerve-cell. In order to verify this dynamic quality of emotion, we need but recall how the individual behaves under any strong feeling. Muscles grow tense, eyes become humid, respiration halts or quickens. The glass of water on the speaker's desk is the acknowledgment of the negative correlation between embarrassment and salivation.

When this energy is working freely, there ensues smooth and efficient bodily progress; but when it becomes blocked or thwarted, so that in amount it exceeds the means for its adequate outflow, then its discharge by way of muscle and gland still occurs, but is less effective in bringing about good adjustment. Here, in simple forms, we see the child who kicks and screams when angry; the impatient adult who drums with his fingers, and swings his foot; the patient's relative who, as a prey to anxiety, "cannot sit still;" the bored listener who fidgets; or (to quote Fisher) the man caught in a traffic jam, who futilely toots his horn, or relieves his nervous tension by profanity.

As Cannon points out, following his well-known experiments on Harvard medical students keyed up to take examination, emotion is a biological means of energizing the individual for violent physical action; and, once the organism is prepared to act, this energy acts as a disturber, if action fails to take place.

With tuberculosis patients, we have ample confirmation of these physiological principles.

In the first place, their bodily activity is checked by enforced rest, which means that the change of environment, available to those of us who can get about, is denied them. We can at least go elsewhere, and do something, to distract our ruffled feelings. The tuberculous person must stay day after day, month after month, right where he is. He cannot walk it off, or work it off! Thus, in tuberculosis, unused emotional energy devastates the organism to a greater degree than with a well and mobile individual.

Tuberculosis is a long-range and deliberate adversary; which means continued financial burden and, nearly always, financial worry. It shifts

relationships between husband and wife, parent and child, lover and beloved, employer and employee: so that at home, and in business, emotional strains are practically unavoidable. Segregation usually emphasizes the problem, as the patient has at the same time leisure for brooding.

Every patient with tuberculosis has, therefore, *ipso facto*, his emotional problem. In the case of patients who are in state and county institutions, this is exaggerated by loss of funds and consequent feeling of humiliation at having to "come on charity."

Whatever pet theories we may entertain as to motives for mental conflicts, it is a practical fact that each one of us needs at least to feel safe, if he is to give his best to the business in hand. Anything which menaces our bodily, mental or financial security, sets up at once a state of tension, which disintegrates our assembled forces in fronting our world. In sensitive individuals, the same conflict arises if their personal or "spiritual" values are assailed. (It is always the "conscientious" who have the nervous breakdowns.) Likewise in the weak and timid person, he who has never learned self-reliance or known what it means to think well of himself by reason of success due to his own efforts, the *sense of his inadequacy* is always his first response. He it is whose self-esteem is so deeply wounded by taking help from others that he can never get away from the fact. To function at his best, he needs to be fortified by security of place, income, reputation; and, failing these props, he retreats behind a proud reserve, or makes loud lamentation. Such individuals are often aggressive and assertive, in the need to prove their worth to themselves and others; hence we invariably find a secret feeling of inferiority behind the mask of the braggart. Those who are completely sure of themselves do not stop to give heed to the matter.

A woman of good birth and social standing was brought by poverty to a tuberculosis ward where Mexican women were her fellow-patients. She felt deeply humiliated, and asserted her superiority by refusing to talk, except for an occasional remark of extreme condescension. Moreover, according to the nurses' report, she drummed upon the bedside-stand to prevent others from sleeping when she herself was wakeful, and annoyed the other women in numerous ways.

On being interviewed, this patient was quick to tell of her former distinction. Her diagnosis of tuberculosis had been made on the very day on which she had been chosen to fill an important post. Back of that were several severe emotional conflicts. The patient said that she had

never known peace. When shown how to face her situation instead of running away from it in phantasy, she was confronted with a long period dating from childhood, in which she was the thwarted and secretly self-distrustful daughter who had never known success at home or abroad. She actually learned confidence and freedom for the first time in that ward, and tasted the sweets of popularity among the Mexican women.

A man, who had for several years been bedfast, suffered keenly from being a county charge. He was educated, and liked to read. He stated that he had misused his opportunities and "figured" that his inability to get well was the price to be paid in consequence. His wife had left him, his only child had grown up estranged, his partner had taken the proceeds after selling out his business: these troubles were gone over and over in his mind. Talk brought out that he had been a timid boy, and later a retiring sort of man whose wife was more resourceful than he. He blamed her relatives for their matrimonial break up, and observed: "I bought two guns, and if I could have got all the relatives together in one room, I would have shot them and myself. *What would my home paper have said to that*!" Here the lack of self-confidence had clearly dated from childhood, causing failure of adjustment, and projecting the blame on others: the emotional tension prevented his progress, although the physical condition was not commensurate with his distressed mental state.

We can afford to disregard for our purpose the question whether feelings primarily determine physical symptoms, or *vice versa*; because, when we focus clearly on the *responses as a whole*, we find that, when the total response is favorable, we have health. When growth factors are misdirected, are thwarting one another, or are being interfered with, ether from within or without, the result is disrupting to the organism. No cell, visceral or somatic, is exempt from possible effects of this interference.

Every physician knows innumerable instances of what anxiety, fear, home-sickness, financial strain, can do to his patient's condition; and, conversely, he is familiar with the statement: "Oh doctor, just *seeing* you makes me feel better!" These are, literally, truths. Something detrimental does happen to all responses of the individual, through worry; something beneficial takes place as inevitably, through the building up of the sense of security.

A recent instance in which reactions were checked objectively through metabolic index, is that of a college student who was uncertain as to

whether she would be able to complete her course. Having posed as a self-assured young person, she would not admit loss of confidence. Her metabolic rate of +134, pulse-rate 112, changed within forty-eight hours to a basal rate of −3, pulse-rate 72. The student meanwhile had been reassured as to financial aid and her own physical and mental ability. To whatever reason this was due, something had taken place in her responses to her situation, so that she not only *felt* more secure, but she *was* more secure.

If metabolic processes are influenced thus, we can see at once that the organism is making some sort of response to some change of its own "inner environment," as Claude Bernard, Walter Cannon, Henry Sewall, and others, have dubbed what is doubtless a delicate chemical readjusting of the blood-stream. Is it endocrinal? Trophic? Due to autonomic nervous system? Vascular and trophic changes are demonstrable wherever strong feeling is present.

For our discussion, does it matter what the immediate aetiology may be, as long as we recognize squarely and clearly the fact that in this disturbance of feeling, which we call *Emotion*, something just as potent as drugs, sera or bacteriological toxins is at work?

Fear is, of all emotions, the one most often found and the most disintegrating to the tuberculous individual. Its bodily symptoms are well known. If concealed, it by no means follows that the fear itself is abolished; rather is the reverse true, according to observations made by the writer on 87 patients under fairly carefully controlled conditions, in a county sanatorium.

A recent study was undertaken with the avowed object of trying to discover whether the toxin of tubercle bacillus was the sole reason why "tuberculosis patients act the crazy way they often do," as the Medical Director put it, where the investigation was made.

Before determining the specificity of the tubercle as the chief aetiological factor in such states of the organism as extreme optimism (*spes phthisica*), depression, irritability, jealousy, cruelty, self-reproach, anger, injury to self-regard, excessive bodily appetites, or any of the numerous "stirred-up feelings," which are commonly accepted as typical of tuberculosis, it is necessary to find out what the responses of nontuberculous persons would be, under conditions which are identical in everything but the specific toxin.

As cancer, to the lay mind, is now joining the ranks of controllable,

if not curable diseases, it should be possible to get objective data as to mental states which would be comparable in cancer and tuberculosis.

In a case illustrating this, in which carcinoma had recurred following operation but the malignant processes were now being held in check by radium, the patient exclaimed brightly: "They all marvel at my being so cheerful; I don't dare be anything else! I just don't ever let myself *think* of not getting well!"

The mental problems of all forms of chronic illness should be subject to study from the dynamic angle. Disorders having the same conditions in common, in which the mobility, personal relationships, and creative outlets of the individual are restricted for long periods of time, together with the metabolic imbalance of a wasting disease, should be scrutinized for emotional symptoms which are also found to be common to the disorders in question. Ways of evaluating these symptoms quantitatively become more available as we learn to think in terms of scientific accuracy.

It is possible to apply laboratory methods to any observable phenomena. Even though measures of precision have not yet been evolved for emotional states, it is a step in the right direction to assemble the evidence, and to compare symptoms involving strong feeling with objective physical findings. Such correspondence can be observed in the physical field, in rise or fall of temperature, in metabolic index, and in functions governed not only by the vegetative nervous system, such as digestion and elimination, but by the sympathetic division of the autonomic as well, including, as Cannon has shown, heart-beat, respiratory change, pilomotor reflex, endocrine activity, increased blood sugar and hormone liberation. To these may be added, as possible signs, the healing or increase of cavitation, and other reparative or destructive processes of the body, as revealed by X-ray and chemical analysis.

It would seem reasonable to ask of any measures, which set out to regulate emotion, that they should prove their validity by producing an effect upon the general bodily well-being of the patient.

Such an attempt was undertaken in 1929–1930, under the auspices of a State Tuberculosis Association, at a county sanatorium having at that time 755 patients. (Reports have been previously made.) Eighty-seven patients were under observation. Although a complete comparison with physical symptoms was not made, it would be possible to check the records of emotional behavior with the extensive and accurately kept physical histories. The net results were in terms of social adjustment, and a few cases will perhaps illustrate the foregoing conclusions.

As a preliminary to this study, it was determined to select cases in which the patient was reported as a disturber of the peace of the ward; or the individual was fretting or despondent; or he would not coöperate; or he was aggressive, and overbold; or in which he was a "nut" or a "pill." (These referred impartially to both men and women patients.)

It was decided to deal only with those whose chances of recovery or arrest were at least tentative; and the following questions were posited for answer:

1: Is the emotional instability of tuberculosis patients due entirely to toxaemia?
2: Is lack of progress in the patient's condition traceable to emotional causes, such as fear, etc.? If so, which predominates?
3: What benefit can mental hygiene bring to patients as to
  a: physical improvement?
  b: mental placidity?
  c: increase of ability to become self supporting?
4: Are patients who give vent to their emotional conflicts more amenable to treatment than those who repress emotion but brood in secret?

Fear was predominant, as the chief factor in emotional instability. It was found to be present, to some detectable extent, in all but two instances. One of these was a patient who had been told that, as "a light case," she would be ready to go home as soon as she recovered from an appendicectomy which had brought her to the acute unit. Her attitude was quietly relaxed, without tension of any sort, either of marked cheerfulness, stoicism, or depression. It was almost startling to find a patient who felt no need of any form of defense against fear. She knew she was getting well, and that her appendix operation was responsible for her clinical symptoms. The other instance was that of a woman whose home conditions had been hard, and who was deeply appreciative of the medical service which the sanatorium afforded. "I think it's wonderful how much they do for us here!" was her verdict. She realized her opportunity for recovery, and that recovery was thereby assured.

Fears wore various aspects, and some disguises. There was bravado, expressed in the young actress, who said: "It's all in the breaks, so what's the use of being so careful? Might as well enjoy life while I can." And, again, the intelligent negress who observed: "I know I'm going to die anyway, and I'm no coward, so I'm going to have a good time while alive." This patient admitted afterward: "No one has ever known how I really feel 'underneath'." There was the deliberate cheerfulness, as

when a young man jested through weeks of optimism, finally to break into tears with the words: "I want to get well so badly, and I'm afraid I'm not going to make the grade; these are the best years of my life, not counting for anything."

There was the fear of going insane, which is a form of suffering equal in force to the fear of dying. Three patients had been reported by the resident physicians as psychotic, and they themselves in each instance were confirmed in the same belief. One was a man who laid his tuberculosis to boyish autoerotic practices which, he had been told, caused tuberculosis. He had infected his wife, whom he deeply loved, with tuberculosis, which in her took acute form; and, feeling that he was thus doubly responsible, his suffering was keen. To this was added the fact that he had tried to confess to the priest but could not bring himself to more than a partial confession, and thereby he had cut himself off by a lie from the offices of his church. In this predicament, he had become morose, developed persecutory ideas, and finally had siezed a fellow-patient while the latter was shaving, and threatened violence if something were not done to relieve his distress. He felt that he was losing his mind, and was indeed about to be committed to a psychopathic hospital. Once his fear state was traced back to its causative factors, and these were shown to have been wrongly interpreted, a load was lifted and this patient not only became calm, but mingled normally with other patients. (It may be noted that this patient was the youngest of four children; his father drank, and the patient was afraid of him as a child and was very dependent upon his mother. His sense of inferiority was accentuated by the fact that he was "never any good at athletics.")[3]

One bed-patient, whose outer door had been locked lest she should wander away, finally uncovered the fear of choking to death. She had worked in an office, stifling her cough, until it became so troublesome to others that she had been obliged to take an outdoor job, as canvasser. Here she had walked daily to the point of exhaustion, and, after admission to the acute ward, was afraid to lie down to sleep because someone had told her that, as she grew weaker, she would be unable to cough up the sputum which collected during the night.

A Greek, who could not read or write English, but who for thirty years had owned his own restaurant until hard times and illness had brought him to be a county charge, grew boastful, aggressive, and fault-finding

[3] These cases were reported in *What Mental Hygiene Can Do for Tuberculosis* (by Mary B. Eyre), *Western Hospital Review*, April, 1931.

(especially with regard to the cooking), and was diagnosed as paranoid, with delusions of grandeur. This proved to be a fear-state, whose components were that the disease was invading his digestive organs; that he would die without seeing his only son; that the other patients would look down upon him. His boastfulness was that of the child, who seeks to show off; the fact of his apprehensions being set at rest by X-rays and extra attention from his physician relieved his criticisms of the food; and his emotional state became stable, with consequent physical improvement.

Fear of facing strenuous conditions in the outside world, with the consequent risk of breakdown, is obviously behind many cases of "hospitalitis." It is most marked in the type of home-protected, parent- or mate-dependent individual, who has not learned early to "accept the adventure of living." The more we strive to turn these patients out of their refuge, the tighter they cling; and the chances of relapse and return are increased through their emotional tension. It would be an economic saving to develop self-reliance in these individuals and to release their inhibitions, before we send them out as physically fit.

A mother-dependent young woman of twenty-five had been very homesick on first coming to the sanatorium, but had become reconciled. Her prognosis was excellent, and it was supposed that she would rejoice when told that she might leave; but her reply showed that she had completely transferred her dependence: "This ward is now Home."

Superstitious fears sometimes play an unsuspected part in retarding progress. One woman whose persistence in wanting to leave the hospital finally culminated in acute physical symptoms of vomiting, rapid pulse, gastric pain, etc., admitted that her horoscope had said that she would die, if ever she were surrounded by sick people or heard any talk of death.

Repression of fear was found in many reserved patients in whom it was unsuspected. In each instance the clinical picture failed to account for lack of progress. To illustrate at random, there was the reticent young woman who was unresponsive to friendly overtures for a long time, finally unbending over a cross-word puzzle, who asked curiously: "Can anyone really get well?"

There was the brooding girl who said that she had been married at sixteen, then divorced ("All the worry and uncertainty got me down"), who, on being assured that she had a good chance of recovery, replied: "You don't know how good that sounds! Gee, I'd like to believe you,—but I can't."

The young engineer, who passed from one magazine to another without

change of expression, at last explained that he read "to forget." He said: "Sometimes this thing catches me when I least expect it. I cannot hope, much as I should like to."

The middle-aged woman, whose taciturnity was belied by her widely dilated pupils and tense posture, after finding relief in talking of her anxiety over her children and the farm she had left, observed shyly: "We are like trees; I guess we're the better for a bit of cultivating."

In each instance, the fact of facing and sharing the fear was beneficial, because it relieved the added tension which repression or disguise requires. However, mere admission is not enough. The patient should have help in rearranging the elements of his problems, in the light of his new attitude. While running away from them mentally, he has been unable to get true perspective. Fear involves distortion of values.

Among the disrupting emotions, one of the chief is hate. A woman whose husband had deserted on learning that she had tuberculosis, leaving her with a debt of $1400 on their store which she worked for two years to pay off, attributed her poor prognosis to this fact, and could not get outside her sense of grievance and vindictiveness.

An elderly woman, who could not get along with her son's wife, found sleep elusive and disturbed, because she could not forget that she had been sent to a public institution in place of being cared for at home. This she attributed to her daughter-in-law who wanted her "put away."

A young widow, who had nursed her husband devotedly, contracted his tuberculosis and entered the hospital three weeks after his death. Her elder children were cared for by her husband's family, but the youngest and dearest she was determined her mother-in-law should never have. Her hatred of this woman seemed to carry over from hatred of the stepmother who had come between herself and her father, in her own girlhood. She said that she had come to hate all women; but, in reality, the strength of this feeling was due to jealousy of those two women who had threatened her supremacy and hence her self-confidence. For months this patient had run a temperature above 101°F. She had given way to outbursts of temper, and was considered to be a spoiled and troublesome person. By permission, she spent the week-end as guest in a private house for the first time in two years. Here she played the piano, read, met other guests at afternoon tea, had a complete change of atmosphere. She also had a chance to overhaul her mental attitude, and face the sources of her animosity. Although the physical fatigue of the trip was considerable, her temperature after returning to the sanatorium was

normal, and remained for a month below 99°. While relapses into her old tantrums sometimes occurred and her progress was fluctuating, she made definite physical improvement in spite of a poor prognosis originally.

No adequate explanation can be offered for changes in temperature which accompany emotional excitement, or its release, other than the relationships indicated by Cannon between the autonomic nervous system and endocrinal activity. (*Bodily Changes in Pain, Hunger, Fear and Rage*, 1915; *The Wisdom of the Body*, 1932.) In *The Wisdom of the Body*, Cannon points out that homeostasis of body temperature is regulated in part by the sympathetic, which also influences the output of adrenal and thyroid and pituitary glands, the governors of muscular tonus, and, indirectly, oxygen intake. Muscular action results in heat production, which warms the blood; shivering, pilomotor reflex and sweating are all heat-regulating devices directed by the sympathetic, which also responds to emotional excitement, of either sudden or long-continued duration. Thus the whole mechanism is in such delicate adjustment that change in any factor could presumably cause imbalance.

What happens to energies which are not adequately discharged in ways which satisfy all that a human being has of aesthetic value as well as of bodily hunger can be illustrated by the following instances:

A pretty little Mexican girl had been a behavior problem in the ward for every known dereliction, except perhaps lying. She and a sister were wards of the court, and had been taken after their parents' death, from a grandmother who was unfit to care for them. This child was affectionate and demonstrative to a degree that made her overwhelming to anyone who gave encouragement; she disturbed the other women and the nurses by her gaiety, her irrepressible activity.

To protect the peace of the ward, this child was placed in a room by herself, and wore mittens to cure her of nail-biting and other monkey tricks common to animals in captivity, so that she was without employment for hands, feet, or any other part of her active little organism except ears, eyes and tongue. Her tuberculosis remained at a standstill in spite of all that medical skill could bring to bear. The Stanford-Binet tests showed her mentality to be somewhat subnormal, although her knowledge of certain words in the vocabulary test was amusing: "Lecture: when doctors and nurses scold you. I know that one, all right."

A well-developed boy of fifteen, mentally normal, had to be in a room by himself on account of contacts. He disliked school, as he had not made a good record. Enquiry as to what he wished to do for a life-work, brought the reply:

"Something exciting!" This lad was a behavior problem, with no outlets for energy.

A young married man, who had been engaged in congenial work, had fallen into unscrupulous hands when his health first began to break. After paying large fees to a nonmedical practitioner, he had invested the last of his savings in an automobile and started with his wife for Colorado, where the young wife had her first haemorrhage. Both were sent back to California as county charges, and for more than two years had been separated by the exigencies of sanatorium rules, except for brief interviews monthly. Although his pulmonary outlook was favorable, this man's mental state was so overemotional that he could not speak without tears coming to his eyes, and sleep and appetite were disturbed. Thanks to the wisdom of a humane and enlightened medical director, it was arranged for these two to move to a cottage near by, where the husband did the housework and cared for his wife, who was bedfast, and both patients made steady progress, at less cost to the county. Needless to say, success in such cases would depend upon the intelligence and coöperation of the individual patients. In this instance emotional tension was increased by enforced separation and anxiety, and was lessened by companionship.

Hospitals and sanatoria, which are run on the narrow margin of organized efficiency and economy, make a difficult environment for the patient who is an individualist. Anyone, who fails to conform, blocks traffic. Sometimes the timid or the inarticulate find it easier to be quiet than to attempt to make themselves understood. A patient with language difficulty, who was eating his heart out with anxiety about himself, had a chart on which was written: "No complaints."

Such failures to interpret one another's feelings are among the casualties of any organized group; but doctors and nurses can never afford to relax their vigilance, and one of the most illuminating points learned by the writer was the frequency of the exclamation: "You don't know what it means to be able to talk to someone who has *time to listen.*"

Outlets must satisfy the inmost aspirations of the individual, and carry on his energy in channels appropriate to his needs. It is not enough merely to tell him to "work off" his excess emotion. It must be used creatively after his heart's desire in some fashion. A young man in college, who was suffering emotionally, exclaimed: "I took a long hike, hoping to walk it off, but I came back feeling worse than when I started out."

Cannon points the way physiologically, by showing the disrupting effects upon an organism prepared by emotion for violent action, if the

physical action be deferred or prevented. He stops at that point. The principle can be carried further, to provide adequate means by which the excited organism *can* find use for the energy which it is prepared to expend, through interests fitted to its intellectual level. This becomes an individual problem.

Much has been written on the control of emotion and on its harmful effects in tuberculosis. To warn a patient against giving way to his feelings, without showing him how to bring about this control, is but to increase his strain; just as to beg him when in great bodily fear, not to be afraid, usually augments his terror.

Reëducation of the patient, in the sense of helping him to understand the sources of his emotional stresses in order that he may know how to re-route their component energy, is the most practical therapeutic aid for the emotional problems of tuberculosis. The individual must first be helped to face his difficulties, and to identify the feeling-habits in himself (usually dating back over long periods) which led to his failure; he must be shown how to substitute new feeling-habits, which will lead to better adjustment; how to rely upon himself, and become emotionally grown up; and finally, how to find adequate constructive outlets for his emotional energy. In bed-patients, these outlets must necessarily be through mental instead of physical channels.

"Wise direction of growth energy" might well be the keynote for a college curriculum.

Articles and papers dealing with these lines of thought are beginning to appear in the journals. A study by Dr. Anita Mühl, entitled *Emotional Trends in Tuberculous Women*, which has just come to the knowledge of the writer, was made on 30 subjects in 1923, and gives a detailed study of relationships between clinical and emotional states. A follow up study by the same author in 1929, *Tuberculosis from the Psychiatric Approach*, includes additional patients, among them 25 children (see *Psychoanalytic Review*, 1923 and 1929).

The Mind in Tubercle, by Dr. Andrew Morland, *Lancet*, January, 1932, alluding to compensation for fear, says: "Fear state has much in common between tuberculosis and war neuroses. Underlying both is the fear of death, and the resulting conditions must be looked on as the reactions of individuals of varying mental make up to this all-pervading emotion." He says further: "This condition (*spes phthisica*) is similar in many ways to the mental state in early general paralysis, in which fear of the dreaded disease may drive the patient to the opposite extreme of arrogance and

bombastic behavior." *What Mental Hygiene Can Do for Tuberculosis*, by M. B. Eyre (*Western Hospital Review*, April, 1931), offers some observations on lack of proof of a specific toxin of the tubercle bacillus in causing optimism, or allied attitudes. Severe emotional conflicts can be posited to account for disturbed bodily states in tuberculosis and nontuberculous persons alike. Moreover there are tuberculosis patients with equally severe conflicts who do not show optimism. It would seem that the more intelligent and philosophical face their prospects with greater clarity. This would seem to be more a matter of training and personality than of a specific toxin. A paper on *Abnormal Mental States*, by Dr. C. E. Shepard, as yet unread by the writer, is in *The American Review of Tuberculosis*, May, 1932.

Many studies have been made attempting to measure emotion and personality in terms of electrical resistance. These may be found in indices of the literature.

Researches on metabolic changes in tuberculosis and in mental states have thrown light on the relation of metabolism to emotion. (Ziegler and Levine, *Influence of Emotional Reactions on Basal Metabolism*, *American Journal Medical Sciences*, January, 1925.)

We may well conclude with a quotation from the Presidential address to the Harveian Society by Sir Thomas Horder, as reported in the *Lancet* for January 23, 1932: "What is empirical today, will become rational tomorrow. It is right because it is useful that therapeusis should continue to push out its antennae in this and that direction, hoping to feel new facts that even pathology has not found."

SUMMARY

1. The human organism responds as a unitary whole to its environment, rather than as separated into concepts of "mind" versus "body."

2. Because man, being animal plus, has a bigger brain, he can within limits choose the direction of his growth-energy and develop his nervous system by use, short of fatigue.

3. Emotion is a form of energy, discharging in muscle and gland. It is essential to recognize the dynamic quality of emotion in tuberculosis.

4. It is essential also to recognize the principles that emotion and preparation to act are brought about by stimulation of the sympathetic nervous system;

5. That the body, when prepared for violent action by the sympathetic, suffers when action is thwarted or postponed;

6. That tuberculosis is a disease peculiarly fitted through its long duration, disturbance of social relations, financial burden, and segregation, to foster emotional stress;

7. That tuberculosis prevents effective discharge of energy through physical activity, and therefore requires re-routing;

8. That fear, anger, hate are the most disrupting emotions in tuberculosis, and that fear is practically universally present;

9. That *spes phthisica* is a disguise for fear, and that the same mental state is present in other chronic diseases having like conditions;

10. That a specific toxin is not essential to produce emotional symptoms commonly attributed to tuberculosis;

11. That it should be possible to compare from the dynamic angle emotional symptoms in all chronic illness, regardless of specific toxins;

12. That in reëducation lies relief and that it is necessary to show the patient how to deal with his emotional problems by tracing their sources; substituting new feeling-habits; and by offering outlets for his energy which shall be satisfactory to him on his own intellectual level.

DISCUSSION

Optimism is useful where it is based upon trust in the recuperative energies within the body and is derived from the defense against fear which the patient tries to run away from by pretending that it does not exist.

Courage and fortitude are forces of tremendous therapeutic value and are among the highest attainments of the human being.

THE GASTRIC FUNCTION IN PULMONARY TUBERCULOSIS[1,2]

SEYMOUR J. COHEN

A review of the literature on the gastric function in tuberculosis shows that, while considerable work has been done on the symptomatology of the gastrointestinal tract, there has been but little on the actual secretion of the gastric juice. That on the secretions shows many conflicting and inconsistent observations. The literature can be divided into two periods, one dating from the earliest observations until about 1916, and the second from 1916 to the present.

The work in the earlier period labored under the handicap of improper diagnostic methods of pulmonary tuberculosis. Many of the earlier investigators, such as Landis (1), Klemperer (2), and Croner (3), stated that the patient comes to the doctor on account of various gastric complaints, and the physician may diagnose the case as pulmonary tuberculosis only after prolonged treatment of the gastric disturbances has failed. Several of the authors speak of a pretuberculous dyspepsia. These reports appeared before the X-ray and modern diagnostic laboratory methods were used. While the patient was developing tuberculosis and walking around with fever, he finally began to complain of gastrointestinal symptoms. He went to his physician, complaining chiefly of stomach trouble and forgot to mention his pulmonary symptoms. Consequently these authors speak of this condition as pretuberculous dyspepsia. To-day, however, through our tuberculosis propaganda, through our antituberculosis campaigns, and through our education of the public, most patients come to the doctor in the incipient stages of tuberculosis before the disease has produced any gastrointestinal symptoms, which are nearly all reflex or toxic.

The study of the actual secretion of the gastric juice begins with the introduction of the classical test-meal by Ewald (4) in 1886. In 1889

[1] From the Research Laboratories of the Chicago Municipal Tuberculosis Sanitarium, Chicago, Illinois.

[2] Read at a meeting of the Pathological Section of the twenty-eighth annual meeting of the National Tuberculosis Association, Colorado Springs, Colorado, June 9, 1932.

Brieger (5) reported 64 cases of tuberculosis in which he studied the gastric secretion. Practically all the patients had fever. He found that normal secretion of the gastric juice occurred in 50 per cent of the early cases, 33 per cent of the moderately severe cases, and 16 per cent of the late cases; and concluded that fever *per se* has no effect on the gastric secretions. Hildebrandt (6) (1889) reported 40 cases and stated that digestion is affected by fever. When he reduced the temperature by antipyretics, free acid reappeared in the gastric juice. He stated that a temperature of 100°F. seems to be the limit for the secretion of free acid in the gastric juice.

Shetty (7) (1889) reported 25 cases of tuberculosis and stated that all showed a normal secretion of free acid regardless of the fever. Rosenthal (8) (1888) found that in early and late tuberculosis the gastric juice contains little or no free acid, although the appetite and digestion appear normal. Croner (3) (1898) reported 36 early cases of tuberculosis in which he found no cases of achlorhydria, but stated that fever has some relation to the diminution of acidity. Robin and DuPasquier (9) (1903) reported 85 cases, of which 48 were minimal and showed 69 per cent hyperacidity, 19 per cent hypoacidity, and 12 per cent with normal secretion. Thirty-seven patients were in the late stages of tuberculosis and showed 27 per cent hyperacidity, 57 per cent hypoacidity, and 16 per cent normal. The authors concluded that the diminution of the acidity in the gastric juice is in proportion to the degree of the disease.

Munson (10) (1905) reported 26 cases of tuberculosis in which he made a thorough study of the gastric secretions, using the Ewald meal. He stated that the small amount of hyperacidity, its occurrence in early as well as late disease, a marked tendency to hyposecretion and achlorhydria, and undisturbed motor power, made up the picture presented by these 26 cases. He further said that fever has little or no relation to the secretion of acid in the gastric juice. King (11) (1910) reported 26 patients in various stages of tuberculosis, and concluded that in incipient cases there is no disturbance of acid secretion, while in the moderate and far-advanced cases there is a tendency toward lowered acidity and motility of the stomach.

Mohler and Funk (12) (1916), in an excellent paper, reported 47 cases of tuberculosis in which they studied the stomach secretions by the use of the fractional meal. In 22 patients with early tuberculosis, they found that practically all had a normal acidity, while in 25 advanced cases 15 showed normal acidity, 8 hypoacidity, one hyperacidity, and one a

psychic achylia. They concluded that tuberculosis causes a definite downward progression in secretion and motility of the stomach from the very beginning; that hyperacidity is rare in the early stages; and that pretuberculous dyspepsia is misnamed, in that it is associated with definite tuberculous infection.

Perla (13) (1926) studied 198 patients with the Ewald meal at the Bedford Sanatorium. He reported that 24 per cent had a normal secretion, 2 per cent hyperacidity, 64 per cent hypoacidity, and 10 per cent achylia. Of the patients having fever, 25 per cent had normal

TABLE 1

		NUMBER OF PATIENT	TYPE OF MEAL	ALL CASES					MINIMAL					MODERATELY ADVANCED					FAR ADVANCED				
				Number	Anacidity	Hypoacidity	Normal	Hyperacidity	Number	Anacidity	Hypoacidity	Normal	Hyperacidity	Number	Anacidity	Hypoacidity	Normal	Hyperacidity	Number	Anacidity	Hypoacidity	Normal	Hyperacidity
1903	Robin du Pasquier	85	E						48	0	19	12	69						37	0	57	16	27
1905	Munson	26	E						10	10	70	10	10	11	27	46	27	0	5	40	40	0	20
1910	King	26	E						8	0	26	37	37	12	8	50	34	8	6	0	50	50	0
1916	Mohler and Funk	47	F						22										25	0	36	60	4
1926	Perla	198	E	198	10	63	25	2															
1928	Brooke	21	F						21	15	15	62	10										
1928	Jäggi	100	E							0	58	42	0		0	65	35	0		0	78	22	0
1929	Torning	150	E						33	9	6	85	0	48	2	4	94	0	69	7	13	80	0
1931	Menzel and Schöffel	100	F											100	7	9	24	60					
									142	6	32	41	21	171	9	35	43	13	142	8	46	38	9
									142					171					142				
Total																							
														455									

secretion, 61 per cent hypoacidity, and 14 per cent achylia. He concluded, therefore, that fever is not necessarily associated with a diminution of acid-secretion; also, that a decrease in hydrochloric acid bears no definite relation to the anatomical extent of the disease, although anacidity occurs more frequently in active bilateral far-advanced disease.

Brooke (14) (1928) studied 39 patients in the King George V Sanatorium, using the fractional meal. Twenty-one patients who had no gastrointestinal symptoms showed 62 per cent normal acidity, 10 per cent hyperacidity, 15 per cent hypoacidity, and 15 per cent achylia.

Jäggi (15) (1928) reported 100 patients in the various stages of tuberculosis, and found that the percentage of acid is much more diminished in the advanced than in the minimal cases. Torning (16) (1929) reported 150 cases of various stages of tuberculosis, and found that 85 per cent had a normal or hypersecretion of acid, 9 per cent a hypoacidity, and 6 per cent achylia. Menzel and Schöffel (17) (1932) reported 100 patients with moderately advanced tuberculosis, 71 of whom had fever. They used the fractional meal, and found that 60 per cent had hypersecretion, 24 per cent normal secretion, 9 per cent hypoacidity, and 7 per cent anacidity.

The results of the various investigators are compiled in table 1 for comparison. The percentage of free acid in the gastric juice is tabulated as follows: Achlorhydria, indicating absence of free acid; hyposecretion, indicating free acid of from 6 to 20; normal secretion, indicating free acid of from 20 to 40; and hypersecretion, indicating free acid above 40. One notes among the minimal cases that the percentage of achlorhydria of the various investigators varies from 0 to 15 per cent; the percentage of hypoacidity from 6 to 70 per cent; of normal secretion of acid from 10 to 85 per cent; and of hyperacidity from 0 to 69 per cent. This same marked variation prevails among the moderately advanced and the far-advanced cases. The marked difference of results of the various investigators indicates chiefly that too few cases were reported to draw any definite conclusions, and that the wide variations in each group of patients can only be smoothed out by the results of a large number of observations. However, these results are presented as facts in our present day text-books on tuberculosis.

The chief criticisms of these investigators are as follows: *1:* They have reported an inadequate number of patients and consequently have failed to rule out the wide variation of acidity of the gastric juice. *2:* Most of the investigators have failed to take into consideration the temperature of the patient at the time the gastric-function test was done. It has been shown repeatedly that fever *per se* will inhibit the secretion of free hydrochloric acid when otherwise the stomach glands are apparently normal. *3:* Most of the investigators, especially those using the Ewald meal, failed to allow the meal to remain in the stomach a reasonable length of time. *4:* A few of the investigators have failed to classify the type of pulmonary tuberculosis in the individual as minimal, moderately advanced, or far advanced, and this is especially true of the earlier writers.

METHOD

At first the standard Ewald meal was used, consisting of two small rolls and one cup of tea, no sugar, cream or butter. It was aspirated at the end of 45 minutes. Recent work has shown that for practical purposes the Ewald meal is just as reliable as any other type of stomach-function test. Cheney (19) in *Oxford Medicine* states, "At the present time, therefore, and at least until much more experience has been acquired with the use of histamine, it

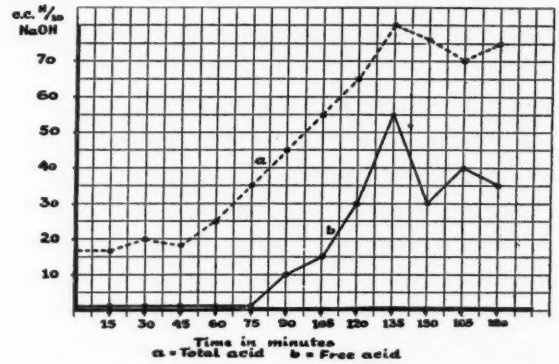


CHART 1. SHOWING FRACTIONAL MEAL ON PATIENT *R. R.*

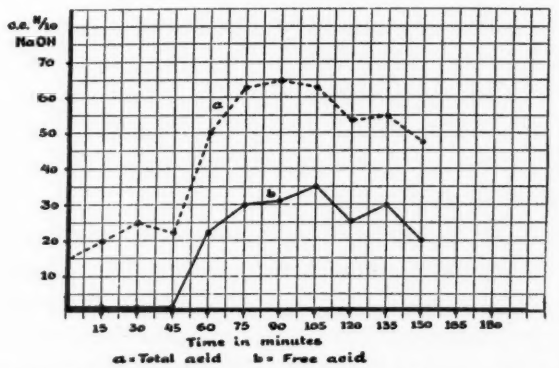


CHART 2. SHOWING FRACTIONAL MEAL ON PATIENT *D. P.*

seems better to prefer the older and longer-tried methods." Gaither (20) (1932) reported from the Johns Hopkins Hospital a study in which he compared the various stomach-function tests (Ewald, alcoholic and histamine tests). He stated that there is ample justification for the continuation of the Ewald meal as a dependable test for the gastric-gland secretion. Even histamine was not found superior to this test. He concluded that bread and water is more of a physiological stimulation to the gastric glands than is a foreign

body. Other investigators (Gorham (21), Wheelon (22), White (23)) have shown that the gastric chyme is not a homogeneous mixture, and that the acidity of various portions of the stomach may vary widely. Therefore, the fractional meal for ordinary purposes does not give any more information than the Ewald meal. After all, the chief point of interest in a stomach-function test is, first, whether the patient has free acid, and, second, whether there is an adequate amount.

About 300 gastric-function tests were made on the same number of patients with the standard Ewald meal. These results were unusual because from 40 to 50 per cent of the patients showed an achlorhydria. This percentage of achlorhydrias appeared much too high because most of the patients, although they were moderately or far-advanced cases, still had very few or no gastric complaints. Consequently, these results were checked by repeating about 25 of these patients with the fractional instead of the Ewald meal. The results of these tests were surprising, and gave definite evidence as to why about half of the Ewald test-meals had shown a lack of free acid.

Chart 1 is a record of a fractional meal on patient *R. R.* The meal was aspirated every 15 minutes. The reader will note that no free acid appeared until 90 minutes, after which time there appeared an adequate amount of free acid. If this meal had been aspirated at the end of 45 minutes, the result would have shown an achlorhydria. In other words, this patient had a long latent period before the stomach glands began to secrete free acid. This result is similar to the one described by Mohler and Funk, and called "psychic achylia."

Chart 2 shows a record of another patient, *D. P.* Here again one notes that the free acid does not appear until 60 minutes have elapsed. Out of 25 fractional meals 11 showed that free acid does not appear in the gastric secretion until 60 minutes or longer have elapsed, while in the rest it appeared after 15 minutes. The most probable conclusion is that these patients with tuberculosis develop a condition in which the latent period for the beginning of secretion of free acid in the gastric juice is markedly increased. These conclusions correspond to those of Sassa (24), who found that the high point of the acid-secretion occurs in tuberculous patients at $1\frac{1}{2}$–$2\frac{1}{2}$ hours, while in normal patients it occurs within 1–$1\frac{1}{2}$ hours. Delhougne (25), using histamine, also reports that tuberculosis causes an increased latent period in the secretion of free acid. The high point of acidity was not reached until 80–90 minutes.

In order to overcome this difficulty, the Ewald meal was modified as follows:

First, the volume was increased from one to two cups of tea; sugar was added and jelly was added to the toast. This made the meal more appetizing and might possibly help stimulate the appetite secretion. Second, the time that the meal was aspirated was increased from 45 minutes to 75 minutes. Third, in order to check the motor activity and emptying time of the stomach, one ounce of raisins with a glass of water was given four hours before the test breakfast. Therefore, when the test breakfast was aspirated, the motility of the stomach was also checked by examining the gastric contents for raisins. In other words, a combined test for secretory and motor activity was done at the same time.

About 1,600 Ewald meals were done, but this report is confined to 1,000 tests. These patients were taken in consecutive order, except that those with a temperature above 99°F. or with any other complication, such as diabetes or syphilis, were eliminated. It has been repeatedly shown by other investigators that fever (6) (18) *per se* will cause a diminution of gastric secretion. As has been stated before, this is an important factor that most investigators have ignored and probably accounts for the diversity of results reported.

Before discussing the results, it would be well to say a few words about the effect of the aspiration on the patient. In over 1,600 patients on whom the Ewald tube was passed, there were, fortunately, no complications, such as spitting up of blood, pain, or coughing spells. The Ewald tube was inserted and withdrawn, the whole procedure taking about 15–20 seconds, only about one or two ounces of the gastric contents being withdrawn for examination.

The contents were filtered through gauze and only 1 cc. of the filtrate was used for the determination of the acidity. It was titrated against N/40 sodium hydroxide. The results, however, were tabulated as the number of cubic centimetres of N/10 sodium hydroxide necessary to neutralize 100 cc. of gastric juice. In addition, the peptic activity of the gastric juice was determined according to the method of Metz, in which he incubates the gastric juice in N/10 acidity with small capillary tubes containing coagulated egg-albumin, and determining at the end of 24 hours' incubation the amount of albumin digested. Normal gastric juice by this method digests about 2 to 3 mm. of egg-albumin in 24 hours at 37.5°C.

The results of these 1,000 Ewald meals, of which 134 were in minimal cases, 530 in moderately advanced cases, and 336 in far-advanced cases, were as shown in table 2.

The patients who showed an absence of free acid had repeated tests in most cases. Consequently, each case of achlorhydria indicates that at least two or more Ewald tests were done on different days and in all cases no free acid was present. From table 2 one notes that the percentage of achlorhydria among these patients averages about 7 per cent and is about the same in all three classes of patients. This is about the normal percentage of achlorhydria that occurs in any other group of nontuberculous patients, as has been shown by various investigators. Eggleston (26) (1931), in discussing achlorhydria, stated that achlorhydria is not an uncommon finding, as it obtains in at least 10 per cent of patients with indications of digestive trouble presenting themselves

TABLE 2

	MINIMAL	MODERATELY ADVANCED	FAR ADVANCED
Number	134	530	336
Achlorhydria	7%	6%	8%
Hyposecretion (6–20)	12%	22%	36%
Normal secretion (21–40)	49%	52%	44%
Hypersecretion (40+)	32%	20%	12%

for medical treatment. Bennett and Ryle (27) (1921) reported a study of the gastric secretions of 100 healthy medical students without symptoms, and found that 4 per cent had achlorhydria. Dahl-Iverson (28) (1924) reported 128 hospital patients, who were nontuberculous but who had undergone various operations and in whom the stomach secretions were examined, showing 12 per cent with achlorhydria. Therefore, the percentage of achlorhydria among tuberculous patients is about the same as in any group of nontuberculous patients. These results correspond to those of Perla, who found 10 per cent of achylia, and Menzel and Schöffel (1931), who found 7 per cent of achlorhydria; but are at variance with Faber (29) (1927), who reported 33 per cent of achylia in all cases of tuberculosis.

Referring again to table 2, one notes that the percentage of hyposecretion varies from 12 per cent among the minimal cases to 22 per cent among the moderately advanced cases, and 36 per cent among the far-advanced cases. The percentage of normal secretion varies from 49

per cent in the minimal cases to 52 per cent in the moderately advanced, and 44 per cent in the far-advanced cases. The percentage of hypersecretion varies from 32 per cent in the minimal, to 20 per cent in the moderately advanced, and 12 per cent in the far-advanced cases. These results, in a large number of patients who were taken in consecutive order and who had a normal temperature at the time of the functional test, show quite conclusively that as the pulmonary process increases in severity there is a gradual diminution in the secretion of free hydrochloric acid in the gastric juice.

The pepsin concentration of the gastric juice in this series of patients corresponded in direct proportion to the free acid. Most of the gastric secretions with achlorhydria showed either an absence or a small amount of pepsin, while those with various degrees of acid showed a corresponding concentration of pepsin.

The results of the motor activity of the stomach, as shown by the ingestion of raisins about 5 to 5½ hours before aspiration, reveal an absence of the raisin-peel in the gastric contents in most of the tests. This shows no retention, and indicates a normal emptying time in practically all of this series of patients.

One hundred and thirty-one patients, who had temperatures between 99 and 102°F. and who were not included in the previously discussed 1,000 patients, were also examined with the Ewald meal. These patients were not classified as to degree of pulmonary disease as the interest was chiefly the effect of fever on the gastric secretion. The results of these observations showed that 24 per cent had achlorhydria and 40 per cent had hyposecretion of acid, while 36 per cent showed a normal secretion of acid. No cases of hypersecretion of acid were found. It will be noted that the percentage of achlorhydria among the patients who have fever is about 3½ times as high as among those without fever, confirming the statement that fever *per se* causes a diminution of acidity in the gastric juice.

One hundred and ninety-two patients who had some symptom of gastrointestinal complaints and who had a normal temperature were examined with the Ewald meal. The results were as follows: 7 per cent achlorhydria; 32 per cent hyposecretion of acid; 41 per cent normal secretion of acid; 20 per cent hypersecretion of acid. Here again the percentage of achlorhydria is the same as in those patients having no gastrointestinal symptoms.

GASTROINTESTINAL COMPLAINTS

The second phase of this work is a discussion of the gastrointestinal complaints of the patients on admission to the Sanatorium. Most of the early investigators have stated that their patients with pulmonary tuberculosis have many gastrointestinal complaints. The ratio of patients with gastrointestinal complaints varies, with the different investigators, from 35 to 92 per cent. Fishberg (30), in his text-book on tuberculosis, states that, as an early symptom of phthisis, dyspepsia is quite frequent. He quotes Hutchinson (1855), who found it present in 92 per cent of his patients; Levison (1905), in 74.6 per cent; and Mohler and Funk (1916), in 64.6 per cent of 1,000 consecutive cases. Janowski (31) (1906) reports 700 cases, of which 35 per cent had gastrointestinal complaints. He states that many of these symptoms disappeared under hygienic treatment. Landis (1910) reported 3,007 cases from the Phipps Institute, and showed that 53.3 per cent of these presented symptoms referable to the stomach. Brooke (1928) reports a series of 80 patients from the King George V Sanatorium, of whom 35 per cent complained of gastrointestinal symptoms. Perla (1926) reports 198 patients of whom 80 per cent had symptoms referable to the stomach.

The results in the case of 1,000 consecutive patients from whom a careful history was taken when they entered the Sanatorium, show that 208 patients, or 20.8 per cent, had some form of gastrointestinal complaint, such as indigestion, distress after meals, bloating, fulness, nausea, vomiting, and various types of abdominal pain. Of these 208 patients with symptoms, 51 (5.1 per cent of total number) had these symptoms years before they developed tuberculosis, and consequently one cannot regard these as cases of pretuberculous dyspepsia. Ninety-seven of these patients (9.7 per cent of total) developed their symptoms months or years after they knew they had tuberculosis. Thus these gastrointestinal complaints were complications of their tuberculosis. Only 60 of these patients (6 per cent of total) developed gastrointestinal symptoms at the same time that they developed tuberculosis. Consequently from these results, one can hardly speak of a pretuberculous dyspepsia.

These results show a much lower percentage of gastrointestinal complaints among tuberculous patients than most investigators have reported. Possibly the most important reason for this difference of percentage is the fact that the earlier investigators were dealing with pa-

tients who did not know that they had tuberculosis, but who went to their physicians chiefly because of their gastrointestinal rather than their pulmonary complaints. Fortunately, however, to-day most of the patients with incipient tuberculosis come to the doctor early in the course of the disease before they have had a chance to develop any complaints referable to the stomach.

SUMMARY

1. As the tuberculous process increases in the lungs, there is a corresponding diminution of free acid in the gastric juice.

2. The percentage of achlorhydria in the various stages of the disease is practically the same, averaging about 7 per cent. This percentage is practically the same as in any nontuberculous group of patients.

3. There is an increase in the latent period for the onset of the secretion of free acid in tuberculous patients.

4. The motor activity of the stomach is within normal range.

5. The pepsin concentration varies in direct proportion with the percentage of free acidity.

6. In patients with fever, the percentage of achlorhydria is about 3½ times as high as in those without fever.

7. About 20.8 per cent of the patients on entering the sanatorium complain of gastrointestinal symptoms. However, only 6 per cent of the patients develop these symptoms at the same time as they develop tuberculosis.

8. The gastrointestinal complaints of tuberculous patients represent complications of the disease rather than symptoms, and consequently one may not speak of a "pretuberculous dyspepsia."

REFERENCES

(1) Landis, H. R. M.: Tr. Nat. Tuberc. Ass'n., 1910, vi, 192.
(2) Klemperer, G.: Berlin. klin. Wchnschr., 1889, xxvi, 221.
(3) Croner, W.: Deutsch. med. Wchnschr., 1898, xliv, 757.
(4) Ewald, C. A.: Berlin. klin. Wchnschr., 1886, xxiii, 33.
(5) Brieger, O.: Deutsch. med. Wchnschr., 1889, xv, 269.
(6) Hildebrandt, C. H.: Berlin. klin. Wchnschr., 1889, xv, 292.
(7) Shetty, F.: Deutsch. Arch. f. klin. Med., 1889, xliv, 219.
(8) Rosenthal, C.: Berlin. klin. Wchnschr., 1888, xlv, 909.
(9) Robin and DuPasquier: Compt. Rend. Soc. Biol., 1903, lv, 743.
(10) Munson, J. F.: New York M. J., 1905, lxxxi, 539.
(11) King, H. M.: Tr. Nat. Tuberc. Ass'n., 1910, vi, 196.
(12) Mohler, H. K., and Funk, E. H.: Am. J. M. Sc., 1916, clii, 355.
(13) Perla, D.: Amer. Rev. Tuberc., 1916, xiii, 317.

(14) Brooke, C. O. S. B.: Lancet, 1928, 215, 1128.
(15) Jäggi, F.: Beitr. z. Klin. d. Tuberk., 1928, lxviii, 511.
(16) Torning, K.: Klin. Wchnschr., 1929, viii, 1261.
(17) Menzel, K., and Schöffel, M. K.: Beitr. z. Klin. d. Tuberk., 1931, lxxviii, 654.
(18) Meyer, J., Cohen, S. J., and Carlson, A. J.: Arch. Int. Med., 1918, xxi, 354.
(19) Cheney: Oxford Monographs, Oxford Univ. Press, 1930.
(20) Gaither, E. H.: Ann. Int. Med., 1932, v, 992.
(21) Gorham, F. D.: Arch. Int. Med., 1921, xxvii, 434.
(22) Wheelon, H.: Ibid., 1921, xxviii, 613.
(23) White, F. W.: Jour. Am. Med. Ass., 1922, lxxix, 1499.
(24) Sassa, T.: Kekkaku, Tokio, 1930, viii, 2.
(25) Delhougne, F.: Deutsch. Arch. f. klin. Med., 1926, cl, 373.
(26) Eggleston, E. L.: Jour. Am. Med. Ass., 1931, xcvii, 1916.
(27) Bennett, T. J., and Ryle, J. A.: Guy's Hosp. Rep., 1921, lxxi, 286.
(28) Dahl-Iverson, E.: Bibliot, f. Laeger, 1924, cxvi, 735.
(29) Faber, K.: Lancet, 1927, ccxiii, 901.
(30) Fishberg, M.: Pulmonary Tuberculosis, Lea & Febiger, 1922, 257.
(31) Janowski, W.: Ztschr. f. Tuberk., 1907, x, 477.

THE BLOOD-PRESSURE IN TUBERCULOSIS

A Study of 230 Consecutive Tuberculosis Patients[1,2,3]

A. R. MASTEN

The 230 cases recorded in this study all had definite pulmonary tuberculosis. Blood-pressure readings were taken once every month during the patients' stay in the sanatorium; but the majority of the readings used are those of the entrance examination and the examination at the end of the period of observation. This period of observation covered from three months to four years, the average being approximately one year. These patients were classified according to the method adopted by the National Tuberculosis Association, into first, second, and third stage. There were 31, or 13 per cent, in the first stage; 24, or 10.4 per cent, in the second stage; and 175, or 76 per cent, in the third stage of pulmonary tuberculosis. Of the 230 cases 130 were females and 100 males. The standard used for determining the normal blood-pressure was the table of average blood-pressures by Dr. J. W. Fisher, as given in the text-book, *Blood-Pressure: Its Clinical Applications*, by Norris, Bazett and McMillan.

On entrance 142, or 61.7 per cent, of these patients were found to be within normal limits, taking normal as being within a range of ten above or below the general average of Fisher. There were 73, or 31.7 per cent, below normal and 15, or 6.5 per cent, above normal. At the end of the observation 145, or 63 per cent, showed a pressure within normal limits, while 62, or 26.9 per cent, showed a low pressure and 23, or 10 per cent, a high pressure. During the period of observation it was found that 92, or 40 per cent, of the cases showed a rise in blood-pressure, and 71, or 30.8 per cent, a fall, while in 67, or 29.1 per cent, the blood-pressure remained stationary. (When the change was less than 4 mm. up or down, it was considered stationary.)

It was found that 76 per cent of the patients who improved clinically

[1] From the Lutheran Sanitarium, Wheat Ridge, Colorado.

[2] Read at a meeting of the Denver Sanatorium Association, Denver, Colorado, May 24, 1932.

[3] All blood-pressure readings were made by the author.

while under observation showed either a stationary or rising blood-pressure. In the remaining 24 per cent who showed improvement, however, there was a fall in blood-pressure. Of the patients showing a definite hypotension on entrance, 42 per cent either died or grew worse during the period of observation, as compared with 20.7 per cent who either died or grew worse among the patients having a blood-pressure within normal limits or higher. Of the hypotension cases, 57.7 per cent showed improvement and a rise in blood-pressure. From general averages, however, the prognosis was twice as bad for a patient having hypotension as for one having a normal pressure or hypertension.

The relation of a gain in weight to blood-pressure was also studied, and it was found that 78 per cent of those who gained weight showed a stationary blood-pressure or a rise. The remaining 22 per cent who gained weight showed a fall in blood-pressure, and it was noted that of those who lost weight 36.6 per cent showed a rise. Therefore, although a gain in weight does not invariably mean a corresponding rise in blood-pressure it seems to accompany it in about the same percentage as it does with clinical improvement; that is, in 78 per cent of the former and 76 per cent of the latter.

The 230 cases were next tabulated in order to determine the relation of temperature to blood-pressure. The results are shown in the following table:

TEMPERATURE	RISE IN B. P.	STATIONARY B. P.	FALL IN B. P.
Normal	28 or 12.1%	18 or 7.8%	15 or 6.5%
Decreasing	34 or 14.7%	23 or 10%	24 or 10.4%
Increasing	30 or 13%	25 or 10.8%	33 or 14.3%

From the figures there appears to be no definite relation between the temperature curve and the blood-pressure reading. This same result was obtained by following several patients over a period of several years by the construction of a chart of monthly temperature and blood-pressure.

Although, as stated above, 61.7 per cent of our patients showed a blood-pressure within normal limits, it was found at entrance that 175, or 76 per cent, had a systolic pressure below the general average for their age, while only 126, or 54.5 per cent, had a diastolic pressure below the average. To determine the average blood-pressure in pulmonary tuberculosis, as well as any value it might have on prognosis, the patients were tabulated according to average pressures for age, sex, and outcome

(that is, whether the patient died or not during the period of observation). Of the 230 patients 36, or 16 per cent, died. The average blood-pressures of these 36 both on admittance and shortly preceding death are shown in table 1.

From this table it seems apparent that the blood-pressures of those patients who died were definitely low, since at practically all ages and in

TABLE 1

Showing the systolic and diastolic blood-pressures at entrance and the end of observation of the 36 patients who died during the period of study

AGE	SEX	NUMBER OF CASES	SYSTOLIC PRESSURE		DIASTOLIC PRESSURE		SYSTOLIC PRESSURE		DIASTOLIC PRESSURE	
			Entrance	End of observation	Entrance	End of observation	Entrance	End of observation	Entrance	End of observation
10–19	F	1	86.0	86.0	58.0	58.0	87.0	91.0	59.0	61.0
	M	1	108.0	96.0	60.0	64.0				
20–29	F	8	104.7	97.8	70.0	69.3	107.1	104.2	72.0	73.0
	M	10	109.2	109.4	73.6	74.4				
30–39	F	5	99.6	101.8	54.8	73.6	106.4	102.3	66.0	74.2
	M	4	115.0	103.0	80.0	75.0				
40–49	F	0					104.5	106.5	72.2	69.0
	M	4	104.5	106.5	72.2	69.0				
50–59	F	0					125.0	111.0	85.0	80.0
	M	2	125.0	111.0	85.0	80.0				
60–69	F	0								
	M	0								
70–79	F	0					120.0	116.0	64.0	80.0
	M	1	120.0	116.0	64.0	80.0				
Total average: 31.3	F	14	101.5	98.3	63.7	70.0	107.4	103.9	70.3	72.7
	M	22	111.1	107.5	74.5	74.4				

both sexes the pressure was over 10 mm. Hg. below the general average, both for the systolic and diastolic readings. In the total average for all 36 cases, who had an average age of 31.3 years, the entrance systolic pressure was 18 mm. below the general average while the diastolic pressure was almost 10 mm. below. It is also noted that practically all of these cases had a definite hypotension on admission to the sanatorium. From

these figures it seems evident that a definite hypotension which does not improve under treatment offers a very bad prognosis. It may be noted, in passing, that the death of these patients occurred, on the average, one and a half years after entrance to the sanatorium.

In table 2 are shown the average pressures for the patients who were still living at the end of the observation period. Here the general average is very little below the normal average for any given age. In the

TABLE 2

Showing the systolic and diastolic blood-pressures at entrance and end of observation of the 194 patients who were still living at the end of the period of study

AGE	SEX	NUMBER OF CASES	SYSTOLIC PRESSURE		DIASTOLIC PRESSURE		SYSTOLIC PRESSURE		DIASTOLIC PRESSURE	
			Entrance	End of observation	Entrance	End of observation	Entrance	End of observation	Entrance	End of observation
10–19	F	7	108.2	115.6	75.4	73.1	112.3	118.5	76.9	74.5
	M	4	119.5	123.5	79.5	77.0				
20–29	F	53	114.4	115.6	77.4	79.8	116.5	118.8	78.7	80.3
	M	36	119.4	123.2	80.6	81.2				
30–39	F	39	114.3	120.4	80.6	82.1	115.8	121.6	79.6	82.5
	M	26	118.3	123.3	78.3	83.2				
40–49	F	11	123.3	128.4	82.5	82.5	123.7	127.6	83.6	86.0
	M	7	124.0	122.0	85.4	88.0				
50–59	F	5	128.4	126.0	78.2	76.0	118.8	115.3	77.2	73.5
	M	4	107.0	102.0	76.0	70.5				
60–69	F	1	110.0	128.0	78.0	80.0	133.0	144.0	79.0	80.0
	M	1	156.0	160.0	84.0	80.0				
Total average: 30.6	F	116	115.4	119.1	78.8	80.4	117.0	120.5	79.8	80.9
	M	78	119.3	122.5	79.9	81.7				

aggregate the systolic pressure is about 5 mm. below the normal average and the diastolic pressure slightly above. Such small variations from the normal averages can be disregarded, I think, for, with our present instruments for determining blood-pressure, it would be hard to obtain readings which did not show as much or more variation. We may conclude therefore that our living patients had a normal blood-pressure; at least, the averages were well within normal limits.

In table 3 the complete record of all patients, both living and dead, is shown. Here the averages are slightly lower than in the tables of the living patients alone, but the difference amounts to less than 3 mm., which leaves the blood-pressures of the patients as a whole still within normal limits. From this it appears that tuberculosis patients in general do not show a definite hypotension, but rather approximate the normal

TABLE 3

Showing systolic and diastolic blood-pressures of the total 230 patients comprising this study, both at entrance and at the end of observation

AGE	SEX	NUMBER OF CASES	SYSTOLIC PRESSURE		DIASTOLIC PRESSURE		SYSTOLIC PRESSURE		DIASTOLIC PRESSURE	
			Entrance	End of observation	Entrance	End of observation	Entrance	End of observation	Entrance	End of observation
10–19	F	8	105.5	112.0	73.2	71.2	110.0	114.3	74.1	72.4
	M	5	117.2	118.0	73.8	74.4				
20–29	F	61	111.9	113.3	76.4	78.1	114.9	116.2	77.5	79.1
	M	46	117.2	120.2	79.0	80.0				
30–39	F	44	112.6	118.2	77.7	81.1	114.7	119.2	78.0	81.5
	M	30	117.8	120.6	78.5	82.1				
40–49	F	11	123.0	128.4	82.5	82.5	120.1	123.8	81.5	82.9
	M	11	117.8	116.3	80.8	81.0				
50–59	F	5	128.4	126.0	78.2	76.0	120.0	114.5	78.6	74.7
	M	6	112.2	105.0	76.8	73.6				
60–69	F	1	110.0	128.0	78.0	80.0	133.0	144.0	79.0	80.0
	M	1	156.0	160.0	84.0	80.0				
70–79	F	0					120.0	116.0	64.0	80.0
	M	1	120.0	116.0	64.0	80.0				
Total average: 30.7	F	130	113.9	116.8	77.2	79.3	115.5	117.9	77.9	79.6
	M	100	117.5	119.2	78.7	80.1				

averages very closely. In this table it is also apparent that in general there is a moderate rise in blood-pressure during the patients' stay in the sanatorium. This same rise was shown even more markedly in table 2, of the living patients; while in table 1, of the patients who died, there is a fall in blood-pressure recorded in practically all instances. These figures also show that the blood-pressure averages are from 2 to 3 mm. lower in females than in males.

The conclusions regarding blood-pressure in pulmonary tuberculosis, as evidenced by this study of 230 patients, are as follows:

1. That the average blood-pressure is well within normal limits.
2. That a definite hypotension which does not improve with sanatorium treatment warrants a poor prognosis.
3. That over 75 per cent of patients showing clinical improvement show a rise in blood-pressure.
4. That over 75 per cent of patients showing a gain in weight also show a rise in blood-pressure.
5. That temperature, *per se*, has no definite relation to blood-pressure.
6. That following a period of sanatorium treatment the average blood-pressure shows a rise.

GENERALIZED TUBERCULOSIS COMPLICATED BY PRESENCE OF YEAST-LIKE ORGANISMS[1]

Report of Clinical History and Necropsy

HENRY W. FERRIS

The literature contains a number of references to local and systemic blastomycotic and similar infections with detailed description of the lesions. Their similarity to those caused by the tubercle bacillus has been pointed out, and the fact stressed that an absolute differential diagnosis rests on the finding of the specific organisms in the tissues (1) (2) (3). The coincidental occurrence of both yeast-like forms and tubercle bacilli has been infrequently mentioned in the literature which I have been able to review. Goto (4) described a case of Turk's in which blastomycetes were found in laryngeal and pharyngeal lesions, and in the exudate of a meningitis. There was also said to be "definite" tuberculosis of lungs and lymph nodes. Montgomery and Ormsby (5), in their review of blastomycosis, mentioned a case with cutaneous ulcers in which blastomycetes were present. The sputum contained tubercle bacilli, but no blastomycetes. Necropsy was not recorded as having been performed. Wade and Bel (6) stated, in discussing the presence of molds in damp living-quarters, that "repeated inhalations of such fungi with their deposit on diseased lung surfaces, as in bronchiectasis, pneumonia or *tuberculosis*, may be sufficient to establish the infection." Their case no. II showed blastomycetes in the lung in giant cells, in endothelial phagocytes, lying free in exudate, or rarely in an uninvolved air-sac. The number, they thought, could not account for the extent of the lesions present. In many of these lesions, acid-fast bacilli could be demonstrated. Rappaport and Kaplan (7) reported a case of generalized *Torula histolytica* infection, in which organisms grew from the cultures taken at autopsy. Tubercle bacilli were stained in large numbers in a fibrocaseous area of one lung. Hansmann (8) and Verse (9) also mentioned a coincidence of the two types of infection.

In view, however, of the difficulty in distinguishing grossly and micro-

[1] From the Departments of Pathology of the New York Hospital and the Cornell Medical School, New York City.

scopically the lesions produced by these two types of organisms, the finding of both together in body discharges clinically, or in tissues at necropsy, makes the differential diagnosis increasingly hard. Consequently I wish to report the clinical history, laboratory findings and results of postmortem examination of a case in which this problem arose.

Clinical History

A. T., a white female, 47 years old, entered the New York Hospital, December 1, 1930, as a private patient of Dr. John H. Garlock. The following history was obtained: Fifteen years previously she began to have attacks of "sore throat." These recurred off and on for nine years, being treated by silver-nitrate applications, with relief for periods of six months to a year. At the end of the nine years, she developed an ulcer on the posterior aspect of her pharynx. In May, 1924, she went to Bellevue Hospital, where the sputum was found positive for tubercle bacilli, and X-ray showed lesions at both apices, suggesting fibrosis. There was a superficial, acutely inflamed, tender ulceration on the posterior pharyngeal wall, extending up behind the soft palate. Smears from this were negative for Vincent's but showed acid-fast bacilli. A biopsy specimen was diagnosed as tuberculosis. The patient remained there three days, going a week later to the Skin and Cancer Hospital, where she remained one and a half weeks. There she was given applications of radium three times. While in that hospital she developed labor pains and returned home, where she was delivered of a dead 7½ months' foetus. The ulcer healed after this, and she gained weight and seemed to be in good health except for a continuous burning in her throat.

Two years later, the right tonsil became red and sore, and she had it "burned out" with medicine. Following this, it remained well for periods of two months at a time. In October, 1929, she saw a physician who said she had an epithelioma and applied nitric acid. Three days later he implanted radium seeds which remained in place seven days. She began to have loss of appetite, with difficulty in swallowing, and lost 30 pounds in three weeks. She went to Mt. Marion for two periods of four weeks each. In May, 1930, she was seen at the Vanderbilt Clinic, where extensive lesions were found in both lungs, with acid-fast bacilli in the sputum, and ulceration of the pharynx and tonsils, diagnosed as tuberculosis. On October 1, 1930, she went to a boarding house in Saranac Lake, under the treatment of Dr. Sidney Blanchet and Dr. George Wilson. No special treatment was given, except that on her own initiative she went to another physician who cauterized her throat once. She complained of a constant taste of yeast. An X-ray of her chest (taken at Raybrook Sanatorium) showed extensive disease throughout both lungs, with cavity in the left upper lobe and localized pneumothorax at both apices.

Dr. Wilson referred her to the Saranac Laboratory for special study, because of the finding of extensive pharyngeal ulceration, without involvement of the larynx. The laboratory findings there were as follows: (1) Acid-fast bacilli constantly in throat smears and in sputum; (2) guinea-pig inoculations of the sputum and of washings from the throat ulcers positive for tuberculosis; (3) budding yeast-like organisms in great numbers in fresh NaOH preparations and in cultures from the throat and from the washed sputum (three examinations of each were made with identical results); (4) voided urine and purulent vaginal discharge gave pure culture of budding yeast-like organisms; one specimen of catheterized urine negative; (5) blood-culture negative; (6) r.b.c. 3,560,000, hb. 48 per cent (Sahli), w.b.c. 11,200, p.m.n. 83.5 per cent, lymphocytes 9 per cent, monos. 3.5 per cent, eosinophiles 2.5 per cent, basophiles 1.5 per cent; (7) Wassermann negative.

No attempt was made to classify the yeast-like organisms from the sputum and throat, but they had briefly the following characteristics: The colonies on Sabouraud's medium were cream-colored, smooth, round, piled up in centre, about 0.5 to 1 cm. in diameter, and larger in original cultures. Cells were round, oval or elongated, varying in size from about 3 to 15 micra. Some of them were distinctly double-contoured, and practically all were budding. In the growth going down into the media, there were some branching hyphae. In the broth there were a few septate hyphae. Otherwise there were no mycelia. There were no aerial hyphae. A guinea pig inoculated intraperitoneally with 1 cc. of 5-day-old pure culture showed no lesions at the end of four weeks. A rabbit similarly inoculated intravenously was alive and well after eight months. A mouse inoculated with 0.5 cc. intraperitoneally was killed after three weeks. The only positive findings were adhesions between the liver and stomach, and abscess-formation in an hepatic gland which yielded on culture a yeast-like organism similar to the one inoculated.

On returning home from Saranac Lake the patient was sent by a physician to the Morrisania Hospital. He told her that she had a fungus growth of the throat, lung and stomach. She remained there three weeks, and was treated with copper-sulphate-carmine intravenously. She entered the New York Hospital from that institution, complaining of dyspnoea, "phlegm in her throat," dysphagia, loss of weight, insomnia, and exhaustion following urination. Physical examination on admission showed a poorly nourished white woman, dyspnoeic, and acutely ill. The uvula, left and right pharyngeal fossae and the soft palate were found eroded and ulcerated. Coarse and crepitant râles were heard over the upper two-thirds of the chest anteriorly and posteriorly. Breathing over the chest was bronchovesicular. The heart-rate was increased. X-rays of the chest showed areas of increased density throughout, more marked in the apical regions. On the left side there was a shadow suggestive of a cavity. The roentgenologist's opinion was that the

apical shadows were suggestive of tuberculosis, but that the lower lung fields were not typical. Urine examination was essentially negative. Red blood cells were 3,950,000; haemoglobin 65 per cent. Differential w.b.c. showed 86 per cent p.m.n. Smears from the throat showed acid-fast rods and masses of apparent yeast cells which also grew on culture media.

The patient died on the second day after admission, having run a fever of 100° to 102°.

Postmortem Examination (No. 7043)

Gross: (Performed 5¼ hours after death.) Body that of emaciated white female, 165 cm. in length. A soft swelling, 7–8 cm. in diameter, on inner aspect of right thigh a short distance below groin, was found to be a lipoma. Inspection of peritoneal cavity revealed nothing of special note. Both lungs attached to parietal pleura by firm fibrous adhesions in posterior portions and especially marked at apices.

Heart: Essentially negative, except for series of peculiar veil-like bands bridging over endocardium of right auricle for about a centimetre and a half proximal to opening of coronary sinus.

Right lung weighed 650 gm.; *left,* 525 gm. They were much the same in appearance and relatively noncrepitant. Externally they were light yellow-grey with prominent pigmented markings. A few of the pleural lymphatics in the lower portions appeared as quite noticeable white streaks. Pleural surfaces slightly roughened, due to old adhesions. A few, millimetre-sized yellow-white nodules just beneath the pleura. On section, upper portions of both lungs, more marked in left than right, showed dense fibrosis, with carbon pigmentation and areas of actual calcification. Few small excavations with thick walls in both lung apices. Lower portions of each lung showed diffuse, rather uniform distribution of small yellow-white nodules, on the whole translucent, and measuring from a fraction of a millimetre to 1 or 2 mm. in diameter. Some of these lesions had fused to give a fine serpiginous appearance. The very basal portions of each lung were less involved, and the pulmonary substance was a bright red.

Spleen: Somewhat pale, with a scattering of small tubercle-like structures, some of which had fused to form larger masses.

Stomach, duodenum and pancreas, liver, gall bladder and bile ducts, adrenals and kidneys presented nothing of note.

Bladder: Contained about 200 cc. of slightly cloudy urine. Mucosa considerably reddened and injected, especially near urethral orifice.

Uterus and adnexae presented nothing of significance relevant to the main pathological changes.

Intestines: Showed nothing of note externally. On opening, however, there was found in the caecum, at ileocaecal valve, a crescent-shaped ulceration with

reddened elevated margins, almost surrounding the gut at this point. Adjacent mucosa much congested. The base of the ulcer showed a fairly smooth, clean, reddened granulation tissue. About 2 to 3 cm. from this ulcer, in the wall of the ileum, there was an indurated area, about 1.5 cm. in diameter, with an irregular central ulceration about 1 cm. in diameter. Some small firm *lymph nodes* in pericaecal fatty tissue.

Oesophagus, larynx, trachea and thyroid appeared essentially negative.

Uvula: Was deviated somewhat toward right, as if pulled by scar-tissue at its junction with remainder of soft palate. Almost whole surface of uvula involved by a yellow, roughened, granulomatous lesion. Anterior surface, free edge, and adjacent posterior surface of remaining soft palate showed same appearance. No tonsillar tissue identified. Permission not granted to examine brain.

Microscopic: Heart showed little of note. Upper part of each *lung* presented much dense fibrosis. A number of bronchioles had necrotic walls with granulation tissue and tubercle-formation. In necrotic débris lining one of the larger of these, which grossly formed a small cavity, large numbers of acid-fast organisms could be seen in appropriately stained sections. Lower portions of lungs contained single and conglomerate tubercles, most of which showed central caseation. These masses had obliterated a large part of the alveolar structure. Giant cells of Langhans type moderate in numbers. A very rare acid-fast bacillus was seen here in the tubercles. In the *spleen* were a few scattered rather typical tubercles, but no acid-fast rods identified. A few disseminated proliferative tubercles were in the *liver*; tubercle bacilli not found. In the *kidneys* no tubercles were found in several sections studied. The *bladder* showed some congestion, and slight increase of lymphocytes in the mucosa, but no granulomatous process. Sections through the *ileocaecal* ulcer presented a granulation-tissue base, with proliferative and caseating tubercles beneath, in musculature and in edges of ulcer, causing a definite thickening of the wall. Ziehl-Neelsen stains revealed organisms in necrotic débris and to a lesser extent in the more proliferative areas of the caecal ulcer. A small *lymph node* attached to the gut was filled by small proliferative tubercles. *Thyroid* not unusual. Section of *soft palate* showed part of the surface ulcerated away, with remaining layer of necrosis and underlying granulation tissue. Tubercles were found scattered in the granulation tissue, and even for some distance beneath the still intact portions of epithelial covering. Several tubercles were present deep down among the mucous glands and in the musculature.

Note: Sections of lesions were stained with eosin-methylene-blue, with silver stains and with Gram's stain, as well as with haematoxylin-eosin and Ziehl-Neelsen stains. In the gram-stained preparations of the soft palate, oval dark bodies with regular outline were seen in small numbers in the necrotic débris

and at a slight distance down in the granulation tissue. They were comparable in size to the yeast-like forms obtained in cultures from the case. A few showed definite budding. A careful search of sections of the lung, spleen, kidney, liver, intestinal ulcer and mesenteric lymph node revealed no definite similar organisms.

Anatomical Diagnosis: Granulomatous ulceration of uvula and soft palate; fibrosis, pigmentation and calcification of pulmonary apices (bilateral), with fibrous pleural adhesions; bronchiectasis; miliary pulmonary tubercles (bilateral); miliary tubercles in spleen and liver; ulcerations of ileocaecal region; fibromyomata of uterus; corpus luteum (left); lipoma of thigh (right); emaciation.

Bacteriological Findings from Necropsy Cultures: Blood from heart: sterile two weeks. Lung: stained films showed many tubercle bacilli and blastomycetes; cultures by Corper's method showed tubercle bacilli; on Sabouraud's medium, blastomyces. Mucus from larynx: many tubercle bacilli in stained film; blastomyces on Sabouraud plates. Urine from bladder: cultures showed staphylococcus and a few blastomycetes. Spleen and kidney cultures of pieces of tissue removed aseptically showed moderate growth of blastomyces.

DISCUSSION

One can only speculate as to the relation between the various lesions, and the finding of the yeast-like organisms in the cultures. It would seem that the essential tuberculous nature of the processes cannot be denied. The histology, while typical, is not of itself conclusive, but the finding of the acid-fast organisms in many of the lesions is very significant. It is true that apparent blastomycetes (or related organisms) were also found on the surface of the soft palate and for a slight distance in the necrotic débris. However, one would think that, if these organisms played a part in the aetiology of the pathological change there, and elsewhere, they would be found in greater numbers, and more evenly distributed throughout the various portions of the lesions, as described in the literature. No such organisms were found in sections of the other organs, though tubercle bacilli were seen in the lung and intestinal lesions. Why positive cultures of the yeast-like organisms were obtained at autopsy from the kidney, which showed no lesions, and from the spleen in which they could not be identified microscopically, though tubercles were present, is hard to say. In the lung they may have been aspirated from the upper respiratory passages, or forced down by handling of the body. Cultures of the blood were negative for the blastomyces. Despite the fact that the usual precautions were taken in obtaining the cultures

from the kidney and spleen, the possibility of contamination cannot be absolutely ruled out. In the pharynx they may have been present in a purely passive rôle, not playing any part in the pathogenesis of the lesions, or they may have played the rôle of secondary invaders, causing to some extent a continuation of the superficial ulcerative process.

It is interesting to note that, of the three laboratory animals injected at the Saranac Laboratory with cultures from the pharyngeal lesion, only the white mouse presented any evidence of infection. This is in contrast to the apparent pathogenicity of blastomyces for laboratory animals. Montgomery and Ormsby (5) found in their series of cases that nine out of eleven in which injections of cultures of the organisms or the pus from lesions were made in laboratory animals gave positive results. In three of these, it was stated that the organisms were recovered from the nodules produced in the animals. White mice and rats, guinea pigs, rabbits and dogs were all found to be susceptible. Guinea pigs and rabbits were used in most instances. In the light of their data, the yeast-like forms found in the present case would appear to be, at least, of low virulence for the two last-named animals, and, judging from the lack of spread in the organs as noted at necropsy, of low if any pathogenicity for man.

I wish to express appreciation to Dr. John H. Garlock for permission to report this case, and to Dr. Helen W. Evarts, of the Saranac Laboratory, for a large part of the clinical history and laboratory data.

REFERENCES

(1) Miller, W. S.: Reticulum of lung. Its similarity in blastomycosis to that in tuberculosis, Am. J. Path., 1927, iii, 315.

(2) Medlar, E. M.: Pulmonary blastomycosis; its similarity to tuberculosis. Report of two cases, Ibid., 1927, iii, 305.

(3) Literature quoted by above authors.

(4) Goto, K.: Blastomycosis, Mitt. a.d. Med. Fakultat d. k. Univ. (Tokyo), 1915–1916, xv, 75.

(5) Montgomery, F. H., and Ormsby, O. S.: Systemic blastomycosis, Arch. Int. Med., 1908, ii, 1.

(6) Wade, H. W., and Bel, G. S.: A critical consideration of systemic blastomycosis, Ibid., 1916, xviii, 103.

(7) Rappaport, B. Z., and Kaplan, B.: Generalized torula mycosis, Arch. Path., 1926, i, 720.

(8) Hansmann, G. H.: Torula infection in man. Report of a case, Boston M. & S. Jour., 1924, cxc, 917.

(9) Verse: Über einen Fall von generalisierter Blastomycose beim Menschen, Verhandl. d. deutsch. path. Gesellsch., 1914, xvii, 275.

THE CLOSURE OF ADHERENT TUBERCULOUS CAVITIES BY COMBINED ARTIFICIAL PNEUMOTHORAX AND PHRENICECTOMY[1,2]

PAUL SLAVIN

The subject for this discussion is adherent upper-lobe pulmonary cavities which fail to close while being treated by artificial pneumothorax alone.

The value of phrenic evulsion as an accessory to pneumothorax in the obliteration of such cavities has been stressed repeatedly in the literature. There appears to be, however, a scarcity of comment on the mechanics of the treatment. The consecutive phases in the closure of the cavity and their relationship to the pressure conditions within the treated hemithorax are barely discussed.

Most writers contend that the effect of the phrenicectomy is based mainly on the rise of the paralyzed hemidiaphragm.

R. W. Matson (1), referring to cases treated by phrenicectomy alone, believes that

> the results of an induced hemidiaphragmatic paralysis are more dependent upon the rise of the diaphragm and the degree of collapse of diseased lung tissue affected thereby, than upon merely placing the diaphragm at rest. The best results have always been associated with a marked rise of the diaphragm and the poorest results have been in those cases in which little or no rise of the diaphragm took place.

O'Brien (2) advises the use of phrenicectomy

> as an adjunct to pneumothorax when adhesions to the lateral wall or apex prevent proper collapse of cavities, especially if the base of the partially collapsed lung is adherent to the diaphragm and it seems that the ascent of the diaphragm into the chest will relax them and allow a continuation of pneumothorax to cause further collapse of the lung.

[1] From the New Jersey Sanatorium for Tuberculous Diseases, Glen Gardner, New Jersey.

[2] Read at a meeting of the Eastern Section of the American Sanatorium Association, Waltham, Massachusetts, October 14–15, 1932.

Edwards (3) admits that "we are not certain of the physiological effect of the evulsion of the phrenic nerve." In the same article he states that "in artificial pneumothorax cases, where adhesions held out cavities in the middle area, the raising of the diaphragm caused the cavity to obliterate without the necessity of cauterizing."

Similar statements associating increased collapsibility of the treated lung with elevation of the paralyzed diaphragm are found in other publications on this subject. The radiograms illustrating some of the publications do not trace the behavior of the cavity during the entire course of compression treatment. They show the treated lung before and after closure of the cavity, without unfolding the ways in which obliteration of the cavity is related to the compression procedures.

In our series of cases treated by pneumothorax with added phrenicectomy the changes in the cavity have been observed by frequent fluoroscopic examinations and serial rentgenograms. A study of those changes shows that induced pneumothorax displaces an upper-lobe cavity downward and inward, provided the cavity is not diffusely adherent to the chest-wall. This displacement is a result of the property of the treated lung to retract under compression toward a fixed point, attachment to the hilum. Along with displacement, compression of the cavity may take place in the same directions. If the cavity is attached to the parietal pleura by string- or band-adhesions with a limited capacity for stretching, and, if one of the adhesions ceases to yield before the cavity is closed, the latter becomes suspended between two fixed points: (1) attachment to the hilum, and (2) attachment to the fixed adhesion. Further raising of the pneumothorax pressure tends to continue compression of the upper lobe toward one of the fixed points. The direction, in which the upper lobe retracts now, is the resultant of two counteracting forces applied to the lobe: (1) tension toward the root, and (2) contraction capacity of the stretched adhesion. With an active diaphragm, tension toward the root dominates, and the upper lobe continues to retract toward the same fixed point, attachment to the hilum. The cavity, held out by a fixed adhesion and unable to recede more from the chest-wall, is pulled by the retracting upper lobe toward the root. Stretching and enlargement of the cavity results. Following paralysis of the diaphragm there is a gradual relaxation of the treated lung and abatement of its tension toward the root. The contraction capacity of the stretched adhesion becomes the prevailing force, and the upper lobe commences to retract in a reverse direction, away from the hilum and toward the second fixed point. Tugging on

the cavity ceases and its compression proceeds toward the attachment to the adhesion. Closure of the cavity is not influenced by the amount of elevation of the paralyzed diaphragm. The latter may descend under high pressures to levels lower than before the phrenicectomy, but obliteration of the cavity continues unhindered.

Demonstration of the following cases is based on the radiographic evidence obtained in each case:

Case 1: No. 11,288; J. S., male, aged 30 years.

Figure 1: April 3, 1930. Shows right upper-lobe cavity, situated midway between mediastinum and periphery of chest, bounded above by clavicle, below by upper border of second rib. Transverse diameter 2.5 cm., vertical 3.5 cm.

Figure 2: August 4, 1930. Pneumothorax 3 months old. Cavity receded downward and inward. This displacement is caused by retraction of the upper lobe toward the root and is made possible by stretching of the adhesion between the lateral chest-wall and upper lateral aspect of cavity. Both diameters are elongated, due to stretching of the cavity downward and inward by the retracting upper lobe. Transverse diameter 3 cm., vertical 4.5 cm. Small basal pleural effusion. Manometric reading -3, $+2$.

Figure 3: February 18, 1931. Pneumothorax $9\frac{1}{2}$ months. Cavity ceased to recede from the chest-wall. Length of adhesion unchanged, its capacity for stretching being exhausted. The attachment of the adhesion to the cavity acts as a fixed point for the pull of the retracting upper lobe. Continued raising of the pneumothorax pressure caused more retraction of the upper lobe toward the hilum with more stretching of the cavity-walls. The cavity is enlarged: its vertical diameter 5.5 cm., horizontal 4 cm. Visible sputum-level in the cavity. Pressures -7, $+4$. Evidently, the permissible intrapleural pressure was exceeded in this case, and the therapeutic pneumothorax converted into a destructive process.

Figure 4: April 21, 1931. Pneumothorax $11\frac{1}{2}$ months, phrenicectomy one week. Cavity obliterating upward and inward by retraction of its outer wall in those directions. Oblong diameter 4.5 cm., its shortening proceeding from the hilar end; transverse diameter 2.5 cm. Length of adhesion unchanged. Diaphragm elevated 2 cm. Pleural effusion decreased. Pressures -2, $+7$.

Figure 5: May 25, 1931. Pneumothorax 13 months, phrenicectomy $1\frac{1}{2}$ months. Cavity obliterating upward. Oblong diameter only 2 cm.; transverse unchanged. Diaphragm elevated 4 cm. Pleural effusion at the same level. Pressures -6, $+4$.

Figure 6: June 30, 1931. Pneumothorax 14 months, phrenicectomy $2\frac{1}{2}$ months. Diaphragm 2 cm. lower than on the previous plate. Cavity almost

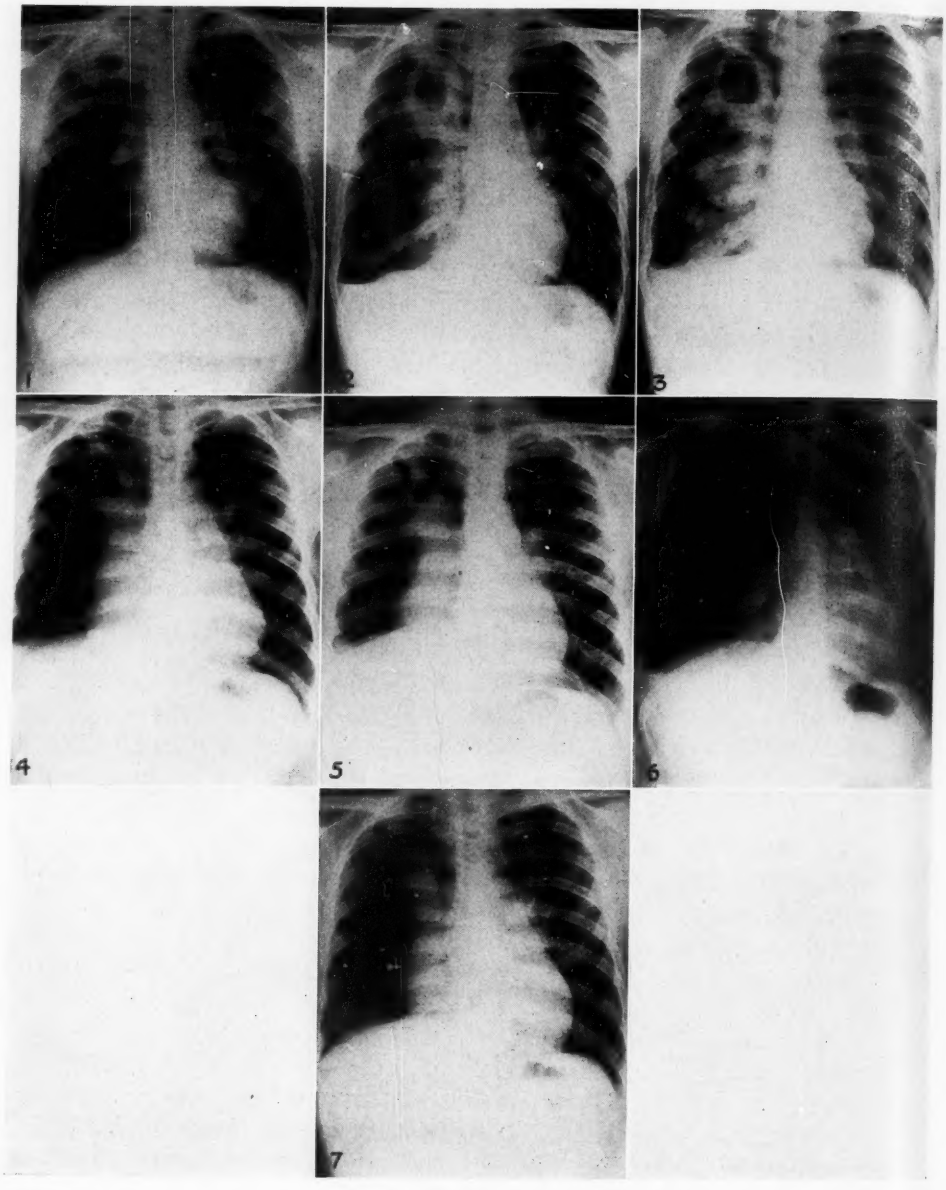


PLATE 1

Case 1: no. 11288; J. S., male, aged 30 years

Fig. 1. April 3, 1930. Fig. 2. August 4, 1930. Fig. 3. February 18, 1931. Fig. 4. April 21, 1931. Fig. 5. May 25, 1931. Fig. 6. June 30, 1931. Fig. 7. July 16, 1931.

closed. Adhesion exposed more, due to retraction of the outer cavity-wall. Pressures −2, +8.

Figure 7: July 16, 1931. Pneumothorax 14½ months, phrenicectomy 3 months. Cavity closed. Diaphragm elevated only 2.5 cm. Manometric reading −2, +8.

Thus, with the diaphragm paralyzed, increased pneumothorax pressures caused compression of the cavity from its hilar aspect toward the attachment to the adhesion. Prior to the phrenicectomy, rising pressures resulted in pulling the cavity-walls from the adhesion to the hilum end and brought about enlargement of the cavity.

Elevation of the paralyzed hemidiaphragm in this case would suggest that the stump of the treated lung has been raised upward, causing relaxation of the adhesion. But, with the adhesion relaxed, its attachment to the cavity ceases to act as a fixed point. Compression of the cavity by the surrounding pneumothorax would then continue toward the only fixed point, attachment to the hilum, and the last portion to obliterate would be at the hilar aspect.

It also must be borne in mind that the plates shown present the inspiratory phase with the paralyzed diaphragm in its highest position due to paradoxical movement, while before the paralysis the diaphragm is during inspiration in its lowest position. Rise of the paralyzed dome, as shown by such a comparison, becomes therefore debatable.

The second case shows still more destruction produced by artificial pneumothorax through traction on the cavity from a fixed adhesion toward the hilum.

Case 2: No. 12,370; T. L., male, aged 30 years.

Figure 1: January 5, 1932. Large left upper-lobe cavity, near periphery of chest, immediately below first rib. Transverse diameter 4 cm., oblong 5 cm. Visible sputum level.

Figure 2: January 14, 1932. Pneumothorax 6 days. Cavity receded inward and downward. Transverse diameter 3 cm., shortened by compression inward. Vertical diameter elongated to 6 cm. Large band adhesion, 1.5 cm. long, between lateral chest-wall and upper lateral aspect of cavity. Amount of retained sputum increased. Beginning basal pleural effusion. Manometric reading −4, −0.

Figure 3: April 5, 1932. Pneumothorax 3 months. Adhesion stretched to 2 cm. Cavity slightly more displaced downward. Transverse diameter 5 cm., oblong 7.5 cm. The cavity is enlarged, being more elongated in the line connecting its attachments to the adhesion and to the hilum. Pleural effusion

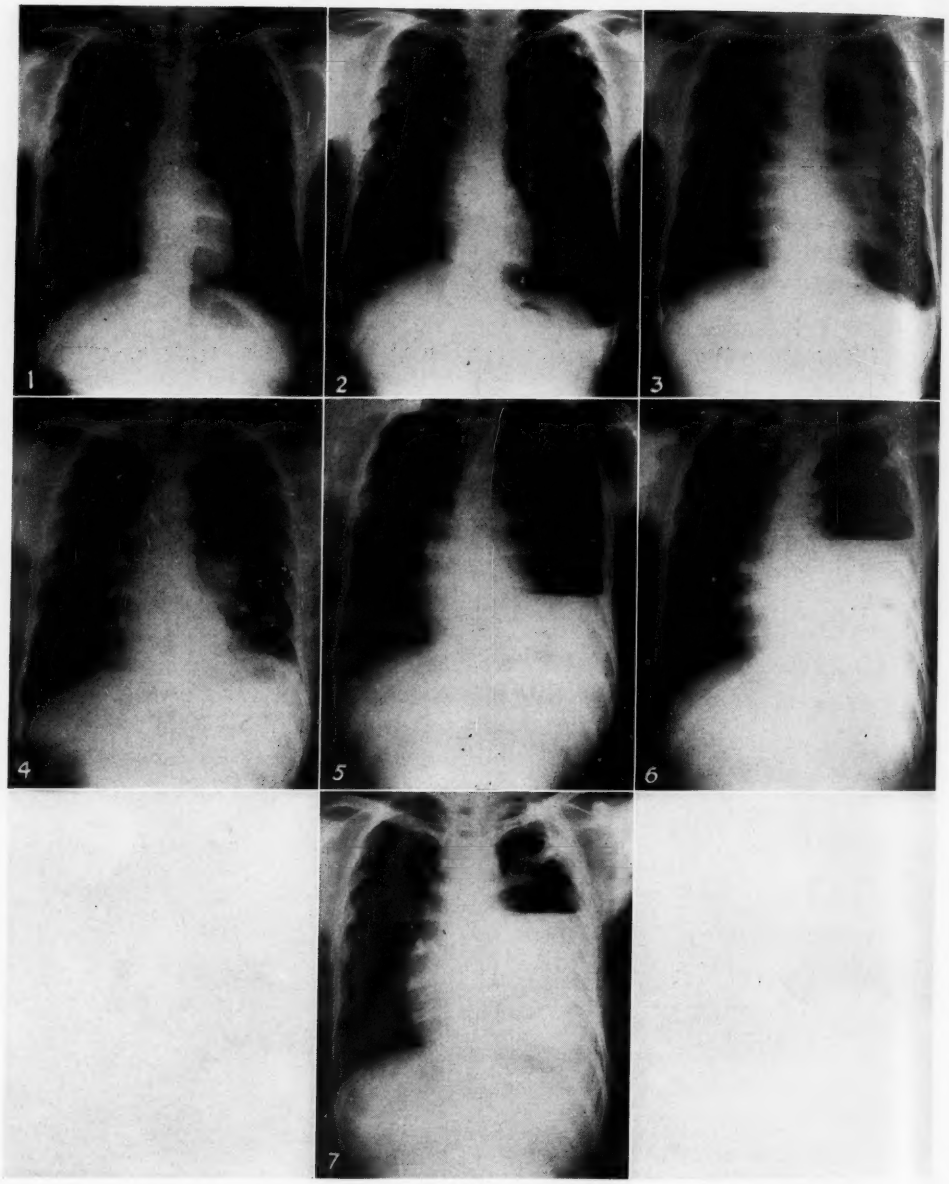


PLATE 2

Case 2: no. 12370; T. L., male, 30 years of age

Fig. 1. January, 5, 1932. Fig. 2. January 14, 1932. Fig. 3. April 5, 1932. Fig. 4.April 14, 1932. Fig. 5. June 21, 1932. Fig. 6. July 22, 1932. Fig. 7. September 20, 1932.

unchanged. Manometric reading −6, −0. Clinically the increased excavation resulted in an increase of expectoration from 2 to 16 oz. and aggravated toxaemia.

Figure 4: April 14, 1932. Two days after phrenic evulsion. Diaphragm elevated 5 cm. Transverse and vertical diameters 0.5 cm. shorter. Pleural effusion unchanged. Manometric reading −6, −0.

Figure 5: June 21, 1932. Pneumothorax 5½ months, phrenicectomy 2½ months. Cavity obliterating upward and inward by retraction of its outer wall in the same directions. Transverse diameter 2.5 cm., oblong 6 cm. Basal effusion at the level of ninth dorsal spine. Manometric reading +2, + 10.

Figure 6: July 22, 1932. Pneumothorax 6½ months, phrenicectomy 3½. Only a small portion of the cavity remaining open at the attachment of the adhesion. Transverse diameter less than 1 cm., oblong 2 cm., its shortening proceeding from the hilar end. Basal effusion at the level of seventh dorsal spine. Adhesion more exposed, due to retraction of the outer cavity-wall. Pressures +3, +7.

Figure 7: September 20, 1932. Pneumothorax 8 months, phrenicectomy 5. Cavity closed. Fluid-level at 7th dorsal spine. Pressures +4, +9.

The presence of a considerable pleural effusion in this case would also suggest lifting of the treated lung and relaxation of the holding adhesion. But here again the cavity is being compressed from its hilar end toward the attachment to the adhesion, indicating that the adhesion is not relaxed and that its attachment to the cavity continues to act as a fixed point.

Further proof that closure of the adherent cavity does not depend on elevation of the diaphragm, is exhibited by the third case, in which an adherent right upper-lobe cavity became obliterated though the paralyzed diaphragm descended to a lower level.

Case 3: No. 12,045; E. C., male, aged 18 years.

Figure 1: June 20, 1931. Right upper-lobe cavity, irregularly shaped. Transverse diameter nearly 2 cm., oblong 4 cm.

Figure 2: September 17, 1931. Pneumothorax 3 months. Cavity displaced inward and downward. Transverse diameter 3 cm., oblong increased to 6 cm. Band-adhesion from dome of chest to upper aspect of cavity. The cavity grew larger under pneumothorax treatment, being mainly elongated in the line connecting the attachment to the adhesion with the hilum. Small pleural effusion. Pressures −8, +1.

Figure 3: November 30, 1931. Pneumothorax 5 months, phrenicectomy 1½ months. There is no inward compression of cavity, but obliteration up-

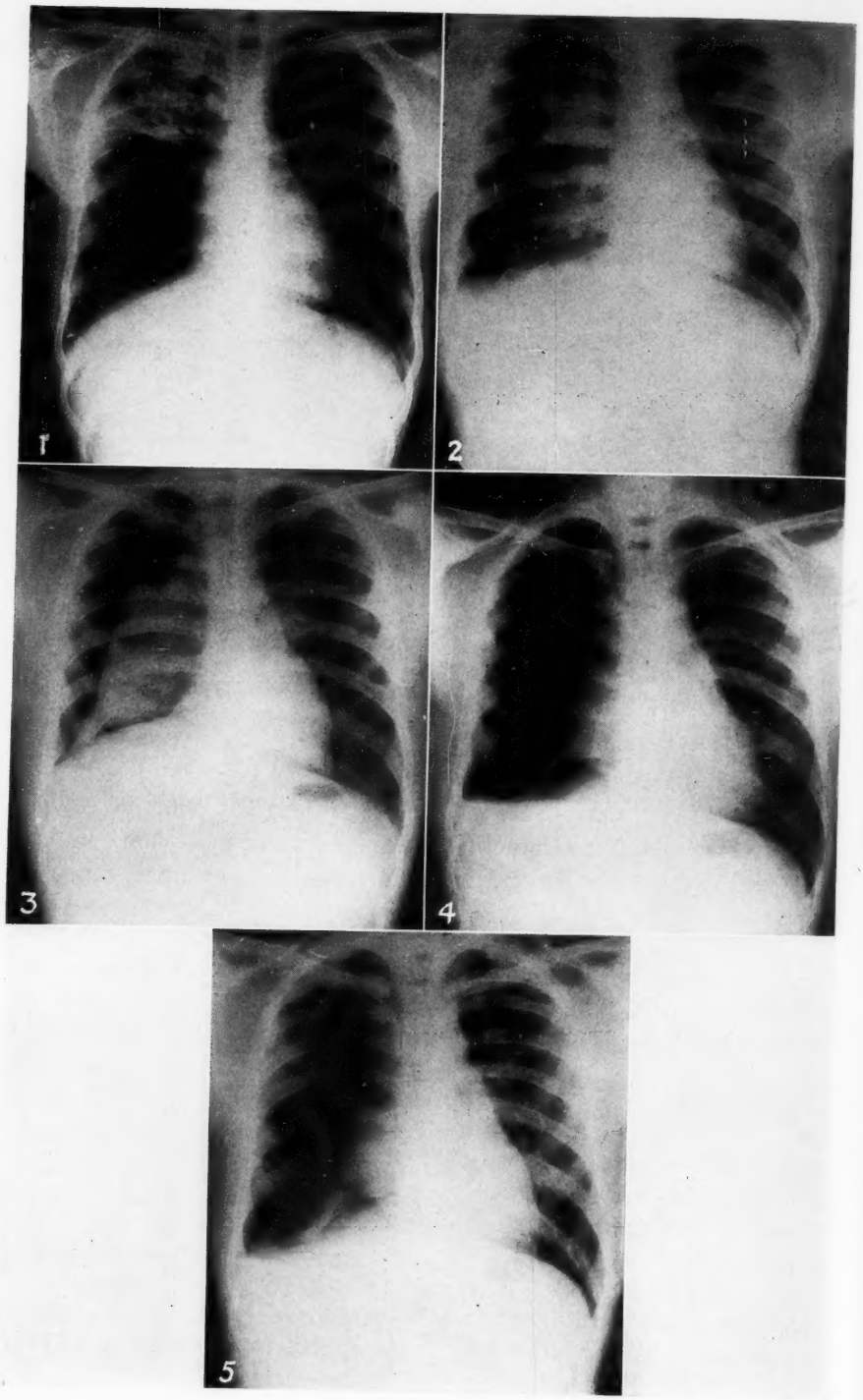


PLATE 3

Case 3: no. 12045; E. C., male, aged 18 years

Fig. 1. June 20, 1931. Fig. 2. September 17, 1931. Fig. 3. November 30, 1931. Fig. 4. February 20, 1932. Fig. 5. March 10, 1932.

ward with the vertical diameter shortened 1 cm. from its hilar end. Diaphragm elevated 2.5 cm. Basal effusion diminished. Pressures −6, +1.

Figure 4: February 20, 1932. Pneumothorax 8 months, phrenicectomy 4½ months. Cavity obliterating upward and inward, its vertical diameter only 2.5 cm., transverse 2 cm. Diaphragm depressed 0.5 cm. lower than before induction of pneumothorax. Pressures +1, +4.

Figure 5: March 10, 1932. Pneumothorax 8½ months, phrenicectomy 5 months. Cavity closed. Diaphragm descended lower than in the preceding figure, being 1 cm. lower than before induction of pneumothorax. Effusion diminished. Manometric reading +5, +8.

There is no ascent of the paralyzed diaphragm in this case to infer lifting of the treated lung. Obviously, elevation of the diaphragm is not responsible for closure of the adherent cavity. It is the additional rest obtained by the treated lung which brings about mechanical changes favorable for moulding of the cavity.

If the cavity-walls are pulled by multiple adhesions in conflicting directions, the obliterative process becomes more complicated and retarded. Eventually, the cavity closes in the direction leading to the attachment of the most resisting adhesion. Such a cavity is represented in the fourth case.

Case 4: No. 12,348; W. G., male, aged 29 years.

Figure 1: December 10, 1931. Right upper-lobe cavity near periphery of chest. Transverse and vertical diameters 6 cm. each.

Figure 2: February 2, 1932. Pneumothorax 1½ months. Multiple string-adhesions from cavity to lateral wall and dome of chest. Cavity displaced and compressed inward and downward. Transverse diameter 3.5 cm., vertical 5 cm. Pressures −5, −1.

Figure 3: March 21, 1932. Pneumothorax 3½ months, phrenicectomy one week. Diaphragm elevated 2.5 cm. Dimensions of cavity same as in preceding figure, though pneumothorax is 1½ months older. Pressures −4, −1.

Figure 4: September 3, 1932. Pneumothorax 9 months, phrenicectomy 5½ months. Pleural effusion at the level of the 10th dorsal spine. Cavity obliterating upward and inward. Vertical diameter 2 cm., transverse less than 1 cm. Pressures 0, +4.

Figure 5: September 24, 1932. Pneumothorax 9½ months, phrenicectomy 6 months. Cavity almost closed. Effusion at same level. Pressures 0, + 2.

To maintain the adherent cavity closed, constancy of the intrapleural pressures is essential. The optimum pressure is determined in each case

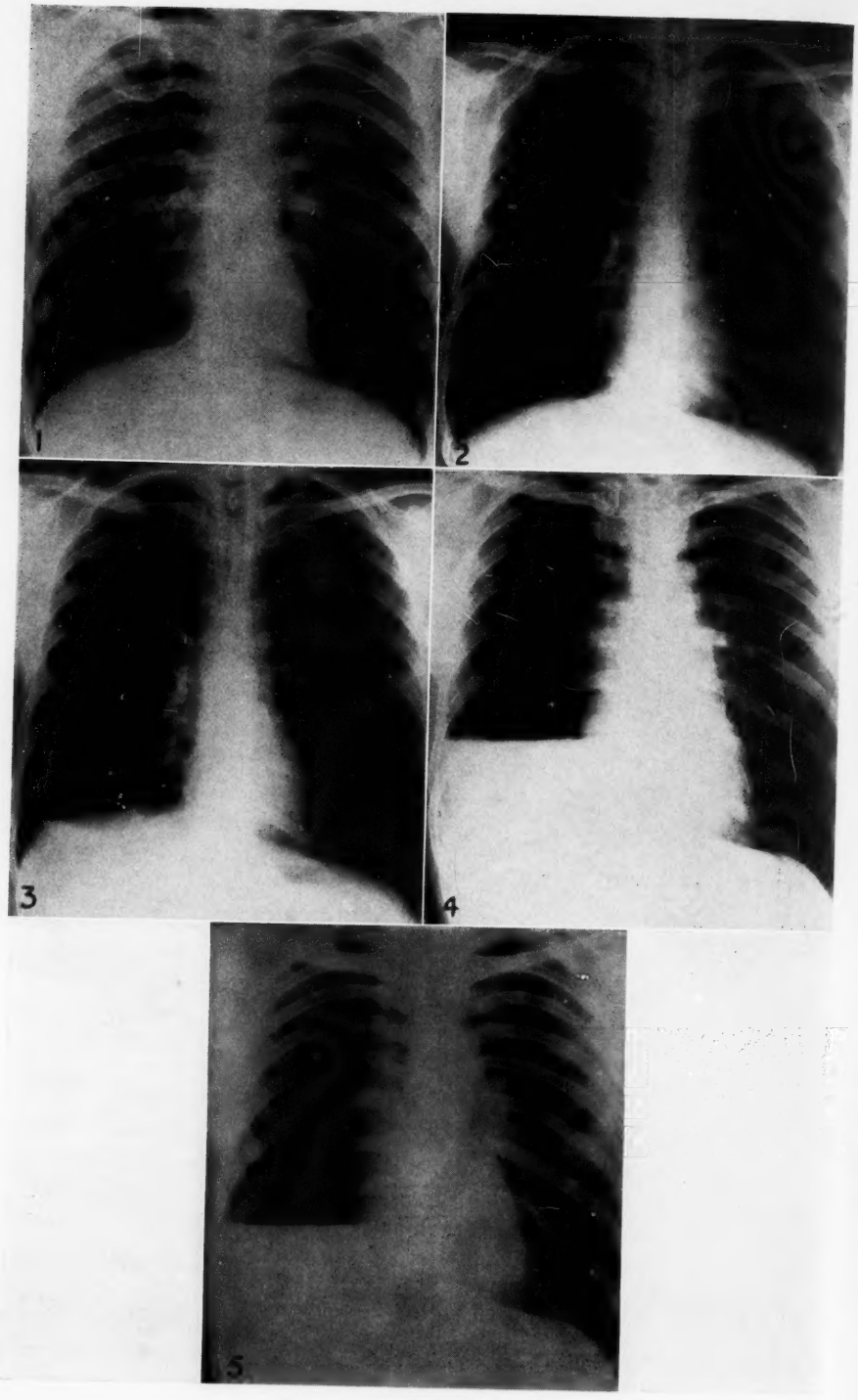


PLATE 4

Case 4: no. 12348; W. G., male, aged 29 years

Fig. 1. December 10, 1931. Fig. 2. February 2, 1932. Fig. 3. March 21, 1932. Fig. 4. September 3, 1932. Fig. 5. September 24, 1932.

and maintained evenly by frequent refills. Pressures lower than the optimum lead to reopening of the cavity. After the latter has remained collapsed for about 3 months, the refills may be given at longer intervals. The cavity is held closed by proper pneumothorax pressures and not by the elevation of the paralyzed hemidiaphragm.

Successful closure of an adherent upper-lobe cavity is accomplished occasionally by a pleural effusion complicating pneumothorax. The factors leading to obliteration of the cavity in the presence of a pleural effusion are probably temporary paralysis of the diaphragm caused by involvement of the diaphragmatic pleura, and constancy of the intrapleural presssures resulting from lessened absorption of the injected air.

Diffusely adherent upper-lobe cavities do not recede from the chest-wall with the induction of pneumothorax. The injected air is prevented from surrounding the cavity-walls and compressing them toward a fixed point. Obviously, paralysis of the diaphragm cannot improve the collapsibility of such cavities.

In our series of 28 cases there were five diffusely adherent cavities, all of which remained open. In 23 cases the cavities were held out by fixed string- and band-adhesions. Eleven of them were left-sided and twelve right-sided. The average length of pneumothorax treatment in those cases preceding the phrenicectomy was 4 months; one case was treated 11½ months. In 18 cases the cavities closed completely, in two they are almost closed, and in three cases, recently operated upon, the cavities grew smaller. After the phrenicectomy, closure of the cavity was accomplished within periods ranging from 1½ to 9 months. The diaphragm became elevated in 19 cases, did not rise in two, and descended lower in two cases. In 3 cases with a nonelevated diaphragm the cavities closed completely. Higher pressures following phrenicectomy were employed in 7 cases, and the same pressures in 16 cases. In one case, far advanced, with bilateral cavitation, death was caused by spontaneous pneumothorax of the contralateral lung. With closure of the cavity expectoration generally ceases and the sputum becomes negative for tubercle bacilli.

CONCLUSIONS

Upper-lobe cavities diffusely adherent to the chest-wall are noncompressible under pneumothorax treatment. Cavities attached to the parietal pleura by fixed string- and band-adhesions can be collapsed by pneumothorax with added phrenicectomy. The rationale of the com-

bined treatment is based on the fact that retraction of the compressed upper lobe toward a fixed point is influenced by two counteracting forces: (1) tension of the lobe toward the root; and (2) contraction capacity of the stretched adhesion. While the diaphragm remains active, tension toward the root dominates, and the upper lobe, suspended between two fixed points, continues to retract toward the hilum. The cavity is pulled from the attachment to the adhesion. Enlargement of the cavity and tearing of the treated lung may take place. Phrenic evulsion is indicated as soon as such enlargement becomes noticeable. Following paralysis of the diaphragm, tension of the lung toward the root gradually diminishes. The contraction capacity of the stretched adhesion commences to prevail and the upper lobe begins to retract toward the attachment to the adhesion.

Elevation of the paralyzed diaphragm apparently plays no part in the obliteration of the cavity. The latter closes in the same manner, whether the diaphragm is raised, unchanged, or lowered. Left-sided cavities close equally well, though the left diaphragm seldom rises to high levels.

After paralysis of the diaphragm a period of several months is required for relaxation of the lung and closure of the cavity, in contrast to the rapid closure obtained by cauterizing the holding adhesions. It must be emphasized, however, that many adhesions are not accessible for cauterization, judging by the X-ray evidence.

The cavity is prevented from reopening by maintaining the optimum pressures at even levels.

REFERENCES

(1) MATSON, R. W.: Exairesis of the phrenic nerve in the treatment of pulmonary tuberculosis, Amer. Rev. Tuberc., July, 1930.

(2) O'BRIEN, E. J.: Surgery of the phrenic nerve and intrapleural pneumolysis, Jour. Am. Med. Ass., February 9, 1929, xcii, no. 6.

(3) EDWARDS, P. W.: Indications for phrenic evulsion and thoracoplasty, Tubercle, 1930, xi, no. 9.

(4) MORGAN, R. N.: Indications for operations on the phrenic nerve, Tr. 26th annual meeting Nat. Tuberc. Assn., May, 1930.

(5) PETERS, L. S.: The compression therapy of pulmonary tuberculosis. A comparative study, Amer. Rev. Tuberc., January, 1929.

(6) MATZ, P. B.: The surgical treatment of pulmonary tuberculosis in the U. S. Veterans' Bureau, Ibid., 1929, xx, no. 5.

(7) MAYER, E., AND LEETCH, H.: Cavities in pulmonary tuberculosis. Rapid contraction of upper and lower lobe cavities with phrenicectomy, Jour. Am. Med. Ass., 1929, xciii, no. 4.

(8) TRUDEAU, F. B.: Phrenic exairesis in the treatment of pulmonary tuberculosis, Ibid., 1932, xcviii, no. 4.

(9) DAVIES, H. M.: Surgery of the lung and pleura, Oxford Med. Publications, 1930.
(10) SEVIER, J. A.: Modern methods of treatment of pulmonary tuberculosis, Jour. Am. Med. Ass., 1929, xciii, no. 13.
(11) O'BRIEN, E. J.: Phrenic nerve operations in pulmonary tuberculosis. Results in five hundred cases, Ibid., 1930, xcv, no. 9.
(12) BRIDGE, E., AND BLY, P. A.: Phrenicoexairesis in progressive pulmonary tuberculosis, Amer. Rev. Tuberc., November, 1929.
(13) HEGNER, C. F.: Surgical rest in pulmonary tuberculosis, Ibid., March, 1928.

THE EFFECTS OF CODLIVER-OIL CONCENTRATE INJECTIONS

A Preliminary Report, with Special Reference to Pulmonary Disease[1, 2]

BURGESS GORDON AND R. J. TITHERINGTON

It is recognized experimentally in rats that xerophthalmia, conjunctivitis and increased susceptibility to infection (in vitamine-A deficiency) and rickets (in vitamine-D deficiency) will disappear following the ingestion of codliver oil (1). In the use of the oil clinically the results are less constant or at least are not easily evaluated. The exception occurs in certain cases of malnutrition, upper respiratory-tract infection, rickets and in rare conditions (xerosis, keratomalacia, etc.) as reported by Pillat (2), Block (3), and others. There is apparently no early clinical picture (in the adult patient) of the submaintenance level of accessory food substances stored in the body. It is possible, because of this, that nutritional disturbances exist for long periods unrecognized. The problem is especially difficult in pulmonary tuberculosis. This is due, in part, to the peculiar variability of signs, symptoms and complications which occur without apparent relation to the extent of infection or the treatment employed. It is not uncommon to observe patients with localized and comparatively quiescent pulmonary infection who experience intestinal manifestations which are due apparently to psychological factors and a sedentary life. These may interfere seriously with an adequate intake of food and result eventually in progression of the tuberculous process. The question arises in the course of events: Are the predominant manifestations the result of nutritional disturbances or the effects of increasing infection? A state exists in the development of the picture when avitaminosis may be entirely masked by the phenomena of the existing disease. Certain experiences suggest that the timely administration of accessory food substances in concentrated form is effective

[1] From the Medical Service of Dr. Thomas McCrae and the Department for Diseases of the Chest, Jefferson Hospital, Philadelphia, Pennsylvania. A part of the expense of this investigation was defrayed by a grant from the Lessing J. Rosenwald Fund.

[2] Read by title at the forty-seventh session of the Association of American Physicians, Atlantic City, New Jersey, May 4, 1932.

as evidenced by improved tissue and muscle tone, increased strength and a sensation of well-being. This consideration seemed of interest because of the striking clinical response in the presence of an apparently fixed status of the pulmonary infection.

In a previous study (4) of tuberculous and nontuberculous patients with histories of long periods of inadequate food intake (normal caloric values but low in dairy products, fresh fruit and vegetables), it appeared, as judged from clinical improvement, that the daily administration of 2 to 3 teaspoonfuls of codliver oil was insufficient for the restoration of vitamine reserve. The figures on probable vitamine storage were largely hypothetical, having been estimated necessarily from the present diets (with supplemented codliver oil) and compared with the intake two to three years before entry to the hospital. It was found in a further study that certain patients in the early series gained in strength and weight when a concentrate of codliver oil equivalent to 6 to 8 teaspoonfuls was administered daily. This high dosage, however, could not be maintained (tolerated) in very ill patients (children and adults) and others with apparent idiosyncrasies to codliver-oil constituents. There was an additional possible factor: in certain instances (chiefly patients with nausea and diarrhoea) the question of incomplete utilization was raised because of vitamine-like substances appearing in the stools (5).

Since the toleration of large doses of codliver oil (or concentrate) orally was not always possible the question of concentrate injections was considered for selected cases. Interest in this was aroused in the reports of Bloch (6) and the experiments of Koehne and Mendel (7), who found that vitamine-A effects were obtained from codliver oil administered subcutaneously. A concentrate of codliver oil[3] was prepared for use in the following studies.

Laboratory Studies

A group of rats on a food intake deficient in vitamine-A substances was selected as follows: 21 animals had severe manifestations of vitamine-A deficiency (stunted growth, weakness, xerophthalmia, loss of hair and respiratory infections). Of these 14 received single subcutaneous in-

[3] This product consisted essentially of a protein-free concentrate of codliver oil, sterilized by the "cold process" and suspended in olive oil. Each ampoule (1 cc.) contained 4,000 units of vitamine-A fraction (three times greater than the content in one teaspoonful of codliver oil) and with high antirachitic values. This was prepared by the White Laboratories, 113 North 13th Street, Newark, New Jersey.

jections (0.5 cc.) of codliver-oil concentrate. The remaining number (seven) received codliver-oil concentrate orally (1 cc.). Five animals with similar manifestations were continued exclusively on a vitamine-A deficiency diet. The findings were as follows: All of the untreated animals died. In the group receiving the concentrate orally three died, and the remaining number showed a gradual disappearance of the vitamine-A-lack manifestations. In the injected group there were two deaths, and the remaining number showed a striking increase in hair, strength, weight, muscle-tone, and disappearance of xerophthalmia. The weight of one animal increased from 108 gm. at the beginning of the experiment to 189 gm. four weeks later. The average increase for the group was 62 gm. in four weeks. The changes were more rapid and constant than in the group receiving oral administrations. The general appearance of 7 rats was so greatly improved three weeks after injection that it was difficult to differentiate them from the "controls" which had been on standard diets since birth.

In further "control" studies the question that the effects were due to some constituent in the oil other than vitamine-A fraction was also considered. Accordingly, 6 rats with signs of vitamine-A deficiency each received one injection (0.5 cc.) of olive oil (low in vitamine-A value). Two gained in weight (10 and 18 gm. respectively) and strength but there was no essential change in the hair or xerophthalmia. This suggested that a certain nutritive influence may have been obtained from the oil, but there were lacking the effects noted in the animals which received codliver-oil concentrate. The remaining rats died without showing any definite improvement. The question that vitamine-D may have influenced vitamin-A in synergistic action (or *vice versa*) was not studied because the former could not be destroyed without also destroying the "A" fraction. In all laboratory studies precautions were taken to prevent the animals from licking the oil from the injected areas.

In the postmortem examinations of the injected animals (killed six weeks after treatment) there was only slight evidence of inflammatory or degenerative changes in the lungs and respiratory tract. The bones showed essentially normal calcification. As judged from the degree of "wheezing" and nasal discharge existing before treatment, a marked influence on the tissues resulted from the injections. In the untreated animals there was widespread metaplasia of the transitional type of epithelium (present in vitamine-A deficiency), as described by Wolbach and Howe (8). The degree of calcification of the bones was less than in

the treated animals. The site of injection was examined in seven animals four weeks after administration. The tissues showed that the oil had been absorbed except in two rats in which there was a residue of brownish pasty material (about 0.05 cc.). In the entire group of injected animals only one abscess occurred. This disappeared as the animal improved. There were no general untoward manifestations which could be attributed to treatment.

Clinical Studies

In a series of active tuberculous (pulmonary) patients (twelve) skin tests were made to determine the possibility of local or general anaphylactic-like reactions. These were entirely absent and the following groups were selected for injections: Pulmonary tuberculosis (far advanced, some with laryngeal and intestinal involvement), 18; pulmonary tuberculosis, minimal or moderately advanced, 9; bronchiectasis, 7; recurring attacks of bronchitis and infections of the upper respiratory tract, 27; osteoarthropathy, 3; surgical (thoracic) convalescent cases, three. The majority of the hospital patients had been below normal weight for more than one year and the various manifestations had not responded favorably to treatment. The ambulatory group was composed of patients with normal weight and those with undernutrition. There had been no essential change in weight or symptoms following a period of management such as could be undertaken at home. Complete physical examinations (including roentgenograms of the chest) of all patients were made before treatment was started. The patients received daily, or three times weekly, subcutaneous or intramuscular (in a few instances) injections of codliver-oil concentrate into the arms (in a few instances into the buttocks). The greatest number of injections in any patient was 57 (in a period of seven weeks); eight patients received 37 to 48 injections; eleven received 26 to 28 and the remaining number varied up to 20.

The local effects of the injections were as follows: In the majority of patients the subcutaneous injections were without untoward effect except for slight transient discomfort (lasting for a few minutes). There were 9 instances of swelling, redness or brownish discoloration lasting two to four days, 7 patients experienced itching for three to four days, and a few scattered "blebs" appeared on the skin in two instances. Curiously, the patients with far-advanced tuberculosis rarely had local reactions, and 7 patients who had manifestations (described) experienced less

severe effects as the treatments progressed. So far as determined, absorption was more rapid and complete than is usually noted in oil injections and not more disturbing than when iron and certain other drugs (and combinations) are employed. Intramuscular administration (buttocks) was used infrequently because of emaciation, tissue sensitivity and the danger of infection (especially in bed-patients). Complete injections of the oil into the muscles of the arm usually caused greater discomfort than when the subcutaneous (in some instances this was undoubtedly partly intramuscular) method was employed. A satisfactory procedure used in the recent cases is as follows: The ampoule is warmed and the oil injected through a 1-in. needle (no. 22) into the firm tissues of the arm at an angle of 45°. The area is rubbed gently for five minutes. Warm compresses are applied for a few moments if swelling or tenderness persist. In every case the plunger of the syringe was withdrawn before injection in order to be certain the needle was not in a blood-vessel. If blood was obtained (rarely) a new site was selected for administration.

In the present stage of the clinical study the influence on disease cannot be evaluated, in part because the patients have not been followed for a sufficient period of time. So far as determined, there has been no change in the tuberculous lesions (calcification or fibrosis), which cannot be explained by the ordinary process of healing. An increase in strength and appetite, and a sensation of well-being and decreased pain in the chest were not uncommon in the ambulatory patients (all conditions) and in the less seriously ill hospital patients (all conditions). The influence on weight was variable (9 showed a gain in weight from 1.5 to 3.2 kg.). In the majority there was no significant change. In patients with upper respiratory-tract infection (including sinus disease and bronchitis) there was a decrease in nasal discharge and expectoration in 11 patients, which could not be attributed to other treatment. There were no favorable effects in bronchiectasis, as judged from expectoration (amount and type), except in one patient (observed in the clinic for over six years) who improved markedly. She gained 2.3 kg. in weight, had less expectoration, and the degree of curvature of her finger nails was strikingly decreased. In the surgical cases there was a rapid increase in strength and appetite. Two patients (tuberculous) with osteoarthropathy had less pain and swelling in the joints than had been experienced in more than six months.

In considering the laboratory data it seems that the utilization of

vitamine-A (in codliver-oil concentrate) is accomplished effectively through subcutaneous administration. This suggests that digestion is unnecessary for the assimilation of the vitamine-A fraction. It appears that the vitamine-D fraction is utilized in a similar manner (as judged from satisfactory calcification of the bones), but in the present study no differentiation was made as to the possibility of calcification being influenced by vitamine-A. The influence of the injections in practically moribund animals was striking. The effects in patients, however, could not be evaluated with any degree of certainty. The impression is that general improvement followed administration. This was characterized by a decrease in the manifestations typical of the existing condition. In the case of intercurrent respiratory manifestations the question may be raised as to the exact state of the mucous membrane. The impression was received in observing several patients that the phenomena were not typical of fresh "colds." If this was correct the decrease in symptoms may be attributed to an improvement in the tissues of the respiratory tract with an indirect influence perhaps on present organisms as well as on new invaders. The study suggests that codliver-oil concentrate injections should be considered in patients who have been unable to take a standard diet (for a long period of time), and who cannot tolerate the oral administration of codliver oil or accessory food substances.

CONCLUSIONS

1. Injections of codliver-oil concentrate were made in animals with vitamine-A deficiency and in tuberculous and nontuberculous patients with possible reduction in the storage of vitamine-A fraction.
2. In the animals there was a decrease in the signs of vitamine-A deficiency following the injection of concentrate.
3. In patients a decrease in certain manifestations occurred following a series of concentrate administrations. So far as determined there was no evidence of specific effect on the tuberculous lesions.
4. The possible value of parenteral administrations of codliver-oil concentrate was considered in patients with low resistance to the existing infection who are unable to tolerate foods rich in vitamine-A values.

We are indebted to Dr. H. T. Mason and Dr. H. L. Stewart for valuable assistance in the laboratory studies and to Dr. John T. Farrell, Jr., for helpful advice in the interpretation of the roentgenograms.

REFERENCES

(1) SHERMAN, H. C.: The chemistry of food and nutrition, The MacMillan Company, New York, 1928.

(2) PILLAT, A.: The main symptoms of the eye in vitamin A deficiency in adults, National Med. Jour. China, 1929, xv, 614.

(3) BLOCH, C. E.: Effects of deficiency in vitamins in infancy, Am. J. Dis. Child., 1931, xlii, 263.

(4) GORDON, B., AND TAI, EN SHUI: Some considerations of the nutrition problem in pulmonary tuberculosis, Amer. Rev. Tuberc., January, 1931.

(5) GORDON, B., AND CAREY, ELIZABETH: A study of blood and secretions of patients on massive dosage of codliver oil. (Unpublished.)

(6) BLOCH, C. E.: Further clinical investigations into the diseases arising in consequence of a deficiency in fat-soluble A factor, Am. J. Dis. Child., 1924, xxviii, 659.

(7) KOEHNE, MARTHA, AND MENDEL, L. B.: The utilization of fatty oils given parenterally, J. Nutrition, 1929, i, 399.

(8) WOLBACH, S. B., AND HOWE, P. R.: Tissue changes following deprivation of fat-soluble A vitamin, Jour. Exper. Med., 1925, lii, 753.

AN APPLIANCE FOR IMMOBILIZATION IN PULMONARY TUBERCULOSIS

S. C. DAVIS[1]

During the past twenty years intensive study by medical men and surgeons all over the world in the treatment of tuberculosis has proved that rest, regardless of how it is obtained, is paramount in tuberculosis.

Everyone caring for tuberculous patients is acquainted with the many different methods of local rest, such as lying on the affected side, lying on pillows, artificial pneumothorax, phrenicectomy, scaleniotomy, and thoracoplasty. All of the foregoing and many other methods of local rest are indicated in special cases.

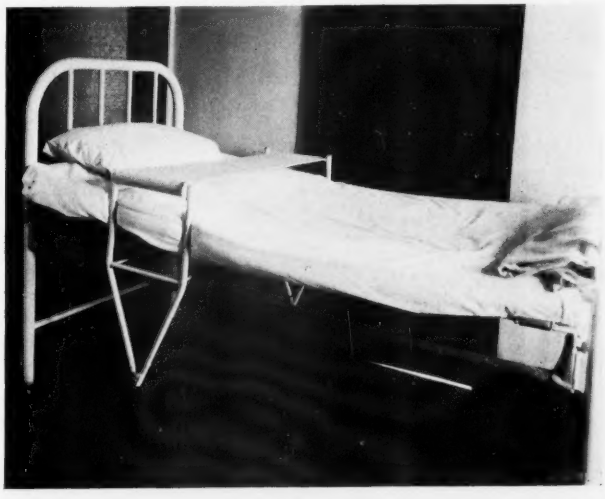


FIG. 1

In 1928 I had a special indication for which none of the foregoing procedures could be applied satisfactorily. I devised an appliance, the description of which can be found in the *Journal of the American Medical Association, August 25, 1928, xci, 565.* It was used in this special case satisfactorily and I have continued using it in many others.

[1] Tucson, Arizona.

However, due to its being uncomfortable because it interfered with movements above the body, I have recently devised an apparatus which patients have called the "Davis hammock," and which I believe will be found very effective in special cases and particularly in those following thoracoplasty, when continued pressure is needed to get the best results from the rib-resection. I have found patients very coöperative in the use of the new apparatus. They realize that they are doing something themselves toward establishing local rest of the diseased area.

A glance at the principle, as illustrated in figures 1 and 2, will show the feasibility of the appliance. I believe that from the cuts shown any good

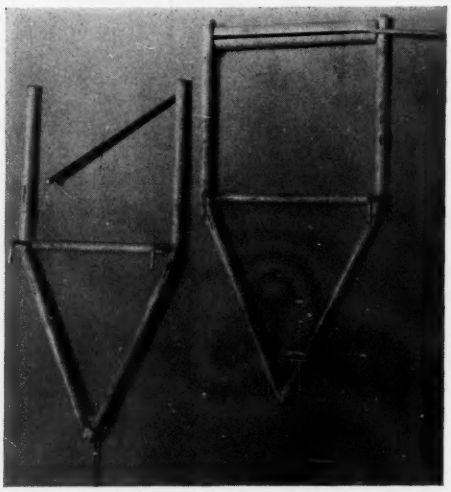


FIG. 2

mechanic will be able to make the apparatus. The weight swings from the bed rails. The cylinder which tightens the canvas is held by a small pin passing through uprights into the flange on the end of the cylinder. (If during the night the patient becomes uncomfortable he has only to pull out this little pin which releases the hammock.) The length of the cylinder is twelve inches. However, in some cases the canvas need be only eight or ten inches, depending on the size of the patient. There should not be too great a lift at first; neither is it necessary to keep any more tension at any time than is necessary to hold the chest off the mattress so that an open hand can be passed freely under the canvas. The cross-bar is easily removed when wishing to make the bed.

TUBERCULIN AND THE SCHILLING BLOOD DIFFERENTIAL COUNT IN THE DIAGNOSIS AND CLASSIFICATION OF TUBERCULOSIS[1]

J. F. BREDECK

Since its discovery by Robert Koch tuberculin has remained a valuable adjunct in the diagnosis of tuberculosis. The subcutaneous tuberculin test, as discovered first by Koch, has continued through the years practically unchanged. He described accurately the local, general, and focal reactions as we note them to-day. We still use the same dosage and the same interval between doses as advocated by its discoverer. We have added little or nothing to his original observations on the local reaction and its significance. Everyone feels to-day as Koch felt, that the local tuberculin reaction when positive is unmistakable evidence of tuberculous infection. He did not think that it was necessarily a sign of activity; nor do we to-day. In recent years there has been much work done in attempts to interpret and evaluate the degree of local reaction in terms of clinical activity. These studies have met with a certain amount of success and also with many disappointments. As a result of them, everyone feels that the intracutaneous is superior to all other forms of tuberculin administration for the study of the local tuberculin reaction.

We find little difference of opinion to-day in the clinical interpretation of the focal reactions that occur in the course of the subcutaneous tuberculin test. Nearly all agree that they are quantitatively specific for tuberculous tissue changes, and of the utmost importance. Some authors go so far as to say that a focal tuberculin reaction is necessarily a sign of activity, but opinion is not unanimous on such a wide assertion as this. All agree also that tuberculous lesions certainly are modified by tuberculin, and cannot be considered as truly healed. Symptoms that are suspicious of tuberculosis with a positive focal reaction are presumptive evidence of active or at least potentially active tuberculous infection. Focal reactions are almost always associated with fever and a general tuberculin reaction. But general tuberculin reactions are accompanied

[1] From the Department of Internal Medicine, Washington University Medical School, St. Louis, Missouri.

by appreciable focal reactions in less than a third of the cases. This leads to the question of methods commonly employed for the detection of focal changes, which, by means of the X-ray, has undergone a refinement of recent years. Even those skilled in detecting focal change by the X-ray admit that this discloses it very little more than careful physical examination. After all, physical examination and the X-ray are rather crude methods for the detection of microscopic allergic tissue reactions at the site of tubercle following tuberculin.

The interpretation of the general tuberculin reaction has probably met with more diversity of opinion than either the local or focal reaction. Some have held for many years that the general tuberculin reaction is of great clinical importance. Others however feel that, unless associated with symptoms and focal changes, it is of little importance; perhaps not of much more importance than the local tuberculin reaction. It has been the experience of all, that even cases of clinically active tuberculosis have failed to show general tuberculin reactions. They believe therefore that such negative reactions do not exclude active tuberculosis.

Since there is little difference of opinion as to the interpretation of the local tuberculin reaction, there may be some good reason for the confusion in regard to the general and focal reactions. We are allowed direct observations on tissues with local reactions, but methods are very indirect for the observation of the focal and general reactions. Perhaps our difficulty could be greatly overcome if we used a more direct method, one that would measure accurately qualitative cell changes. Such a method is available in the Schilling blood differential count.

In 1904 Arneth published his exhaustive studies on neutrophilic leucocyte changes in tuberculosis. His original classification of cells was, at first, almost certain to meet with difficulty, and it has since proved to be impracticable for routine studies. However, we owe a deep debt of gratitude to Arneth for his most valuable contributions to the study of tuberculosis. Numerous modifications of his method have been suggested, of which probably the simplest and most practicable is that devised by Schilling in 1911. In the latter we have all of the cells enumerated in Arneth's differential count. The neutrophiles are divided into what Schilling believes the important pathological forms; namely, myelocytes, *jugendliche*, and *stabkernige* cells, and the normal or segmented forms. He further believes that a true appraisal of degrees of infection is measured more accurately by the degenerative and regenerative neutrophilic shifts than by the relationship of the pathological to the normal

forms, called the *nuclear-shift index*. Numerous observers have compared the Schilling with the various other modifications of the Arneth differential count, such as suggested by Bushnell and others,—some by taking the number of *stabkernige* cells (neutrophilic degenerative shift) in the Schilling count, and showing that it does not measure the infection as accurately as the modified Arneth index of Bushnell. Such comparisons are obviously impossible, as one must at least compare "likes." If one wishes to compare the sensitiveness of the Schilling count with the modified Arneth index, then one must use the Schilling nuclear-shift index, and not the Schilling neutrophilic degenerative shift for comparison. They are not the same, and are therefore not comparable. Schilling has given the nuclear-shift-index value, that is, the ratio of pathological forms of neutrophiles (myelocytes, *jugendliche* and *stabkernige*) to the segmented forms as one to sixteen. This important point of comparison seems to have been overlooked by some observers.

Following the work of Arneth and Schilling, and other European observers, we have had some important contributions in our own country, particularly by Sabin, Cunningham, Doan, Wiseman, and Medlar. All these workers have pointed out the value of the blood differential count in tuberculosis. Sabin and others have emphasized the significance of the monocytes and the lymphocytes. On the other hand, Medlar has advocated the importance of the various leucocytes, particularly the neutrophiles, and their rôle in tuberculous lesions. He has proposed the Ehrlich differential count together with the total count, and analyzed cases by following the total number of the various leucocytes rather than their qualitative changes.

A number of other workers have reported their observations of the blood differential count in active tuberculosis. Most of them have been concerned with the total number of the various leucocytes, with special emphasis on the monocytes and monocytic-lymphocytic ratio. Nearly all of the observations have been made on active cases of tuberculosis and but few on blood changes following tuberculin. This article concerns itself with further observations on the subcutaneous tuberculin test with methods originally published in the AMERICAN REVIEW OF TUBERCULOSIS in July, 1929.

In my experience, the Schilling differential blood count is superior to the total number of various leucocytes as a measure of activity; that is, that qualitative changes among the neutrophilic leucocytes are more important than total numbers of neutrophiles. During the past year,

Wiseman's work on the age of the lymphocytes has promised us much-needed help. His method of differentiating the lymphocytes emphasizes again the superiority of qualitative changes over total numbers, and offers a method comparable to differential counts of the neutrophiles. We shall probably modify our ideas considerably on lymphocytic reactions in tuberculosis when we apply these studies to differential blood counting, as also perhaps our ideas on the monocytic-lymphocytic ratio. The possibility of measuring qualitative changes among the monocytes in our differential counts may also open up other new channels heretofore disregarded.

With these ideas in mind, I have thought it of value to restudy the subcutaneous tuberculin test. During the past six years I have used the Schilling differential count to interpret the subcutaneous tuberculin test. The method permits us to study the cells in the circulating blood that are associated with tubercle. It has been very valuable in explaining some of the differences of opinion as to the value of the subcutaneous tuberculin test. It is a method, at least, that studies cellular activity of the blood under the influence of induced focal as well as general tuberculin reactions. The introduction of a successful method of this kind in studying such a perplexing mechanism as the tuberculin reaction would supply a long-felt need.

In what follows I wish to present the results of the Schilling differential count as observed in 305 cases in which the subcutaneous tuberculin test was used. An anlysis is made of the various types of cases, all of which were under observation for two years or longer following subcutaneous tuberculin tests. The conclusions are based upon the actual observations made on the cases reported.

METHOD

It is not my purpose here to go into details of the Schilling differential count, nor to give specific examples of the changes following tuberculin. The details of the count can best be obtained from Schilling's book. The types of blood reactions following tuberculin have been fully described in my previous article, mentioned above. It is necessary here to emphasize only a few points for the sake of clarity. The tuberculin used in all of these cases was standardized Old Tuberculin, so that 10 mgm. was a minimum lethal dosage for a 250-gram tuberculous guinea pig. All injections were given intracutaneously in the forearm. Differential counts of the leucocytes were made on the day of the injection of

Old Tuberculin and at twenty-four- and forty-eight-hour intervals following injection.

The smears were on slides and Wright's stain was used routinely. Only occasionally were other stains employed. Supravital stains were not deemed necessary to differentiate lymphocytes from monocytes, for my experience has been that for human blood a good Wright's stain, with proper technique, is satisfactory for this purpose. In rabbits and guinea pigs the case is quite different and the supravital method becomes indispensable for doing differential blood counts.

A positive reaction in the neutrophilic degenerative shift in this series means an increase of at least 6 *stabkernige* cells above the number before tuberculin was applied: five were considered the upper limit of normal. A positive nuclear-shift index was considered as one to fourteen or more, the normal being one to sixteen. In this series, the normal lymphocytes were regarded as between 25 and 30 per cent of the total leucocytes, so that above 30 per cent was considered an increase, and below 25 per cent a decrease. Following tuberculin, a positive reaction among the lymphocytes was represented by a drop of ten in the percentage of the lymphocytes. Monocytes were considered normal if between 4 and 8 per cent, and an increase above 8 per cent constituted a definite increase. Again, a reaction was considered positive when the monocytes rose at least four above the upper limits of normal as shown before tuberculin was administered. A reaction of the various leucocytes occurred in over 85 per cent of the cases in the first twenty-four hours, and in 15 per cent in the second twenty-four hours. As a control, the blood was followed until it returned to the figures obtained before tuberculin was administered, which usually occurred in seventy-two hours although in a few instances it took four or five days. This control was used to determine whether activation of the tuberculous lesions followed the injection of tuberculin. All cases were carefully observed for any active infection that might have occurred during the test, and, if any doubt existed, the test was repeated. When the blood reactions were not distinct they were called negative.

ACTIVE CLINICAL TUBERCULOSIS

In this group of 41 cases of pulmonary tuberculosis we wish to consider only patients that were definitely active clinically at the time the Schilling count and the subcutaneous tests were performed. All had been under observation at least two years after the first examination, and

diagnosis and tuberculin tests were made, so that any possibility of error might have been corrected during the period of observation. Of these forty-one, six were advanced, three moderately advanced, and thirty-two incipient. In a few instances, lymph-node and extrapulmonary tuberculous lesions were found. No reasonable doubt could be entertained as to these patients having active clinical pulmonary tuberculosis.

The Schilling count showed only one constant feature, namely, a degenerative shift of the neutrophilic leucocytes, as evidenced by an increase in the number of *stabkernige* cells. This was associated with an increase in the nuclear-shift index. Without exception, all cases in this group of active clinical tuberculosis showed a degenerative shift, and even when the total number of neutrophiles was normal.

In none of the forty-one was there a regenerative blood picture, that is, one with an increase in the number of *jugendliche* cells. Since they are usually too ill, such cases are not suitable for a diagnostic tuberculin test. Having established clinically that all of the 41 cases had active clinical tuberculosis, we have formulated with the Schilling count our first major premise, namely, that *all active cases of clinical tuberculosis show a degenerative shift to the left of the neutrophilic leucocytes with the Schilling blood differential count.* Changes were found among the eosinophiles and the basophiles, but these were not considered sufficiently regular to be of value. There were also changes among the lymphocytes and monocytes, and their tabulations are to be found in table 1 (A). An increase in the monocytic-lymphocytic ratio was not a regular finding; neither was an increase or a decrease in the number of lymphocytes constant. The same thing holds true for the monocytes. The changes among the lymphocytes and monocytes could therefore not be accepted in this series as sufficiently constant and uniform to be of diagnostic value in themselves.

With reference to the reactions of the lymphocytes before tuberculin was injected, we find that twenty-nine, or 70.7 per cent, showed an increase. In 5 cases, or 12.2 per cent, there was a decrease in the number of lymphocytes. In all, there was a change in thirty-four, or 82.9 per cent, of the cases. In 7 cases, or 17.1 per cent, there was no change. The qualitative changes among the lymphocytes, as described by Wiseman, were not studied in this series. At present work is under way to study the qualitative changes among them, according to the method of Wiseman; and there are indications that qualitative changes among the lymphocytes will possibly be as important as those among the neutro-

philes in differential counts. (I wish at this point to express my deep appreciation to Dr. Wiseman for his coöperation in aiding my studies of the lymphocytes.)

In regard to the reactions among the monocytes, 17 cases, or 41.2 per cent, showed an increase, and twenty-four, or 58.5 per cent, a normal or slightly subnormal figure. As for the monocytic-lymphocytic ratio, 8 cases, or 19.5 per cent, showed an increase. These figures differ somewhat from the statistics on active clinical tuberculosis published by others, whose types of cases examined were possibly among groups showing a higher degree of activity than the ones reported in this series. On the other hand, the ratio disturbance between the monocytes and the lymphocytes may possibly depend more on the lymphatic reactions than on the monocytic reactions. In this particular series the lymphocytic reactions were favorable in a high percentage of the cases, as evidenced by an increase in the lymphocytes. In table 1 (A), one can certainly see that the changes among the lymphocytes and monocytes do not even approximate the figures that were obtained among the neutrophiles.

We next have to consider those reactions observed after the subcutaneous tuberculin test. In table 1 (A) the changes noted after tuberculin represent deviations from findings before tuberculin. They do not represent abnormal bloods alone. They therefore represent an exaggeration or further change of the blood findings induced by tuberculin. We gave 10 mgm. as the initial dose of tuberculin in 39 of the 41 cases, or 95.1 per cent. Our studies with the blood differential count, together with X-ray and physical examinations, have made us feel safe in this procedure. The two receiving less than 10 mgm. of Old Tuberculin as the initial dose were incipient cases. No ill effects were noted after seventy-two hours in any patient. All patients had a moderate to marked local reaction. Thirty-four, or 82.9 per cent, had a rise of 1°F. or more in temperature, with symptoms usual in the general tuberculin reaction. X-ray examinations to determine focal tuberculin reactions were not made routinely. In approximately 23 per cent of the cases, induced focal reactions were found on physical examination. Hence, physical examination and the X-ray were not considered sufficiently sensitive when compared to the Schilling count in determining induced focal activity.

It is noteworthy that seven of the forty-one (17.1 per cent) failed to show a general tuberculin reaction, as evidenced by a rise of 1°F. and general symptoms. One of these died sixteen months later of tubercu-

lous meningitis, while another had an artificial pneumothorax eight months later. In both cases the diagnosis of tuberculosis was questioned for some time, but later developments proved it to be active pulmonary tuberculosis. The other five, fortunately, are, with one exception, doing well. The exceptional patient has had occasional haemoptysis. These 7 active cases that failed to get a general tuberculin reaction are in accord with the findings of others. None of them had focal changes shown by physical signs following tuberculin. All showed a moderate to a severe local reaction to subcutaneous tuberculin. Certainly X-ray and physical examinations did not reveal a very high percentage of induced focal reactions. The rise in temperature and general tuberculin reaction failed in 7 definite cases of active clinical tuberculosis, so that they cannot be considered reliable findings with which to measure focal tuberculin reactions in active clinical tuberculosis.

With the blood findings so constant in active clinical tuberculosis, it was deemed highly advisable to study the blood changes following the subcutaneous tuberculin test. In observing the blood differential in these 41 cases it was thought advisable to tabulate the changes among the neutrophiles, lymphocytes and monocytes, separately and combined. In table 1 (B) the changes in the neutrophilic leucocytes following tuberculin mean a shift to the left, as evidenced by an increase in the number of *stabkernige* cells, and changes in the lymphocytes mean a drop in the number of lymphocytes, but changes in the monocytes mean an increase in number of monocytes. In table 1 it can also be seen that all of the cases reacted to tuberculin, according to the Schilling count. In no instance was there only a monocytic change. All cases, however, showed either an increase of *stabkernige* cells or a decrease of lymphocytes following tuberculin. If we use the increased number of *stabkernige cells* and a fall in lymphocytes as our index of induced focal reaction, we find this present in all of the cases. Even those that failed to get a general tuberculin reaction showed this change.

I feel that as a result of these observations on tuberculin in cases of active clinical tuberculosis we have established our second or minor premise; namely, that *all cases of active clinical tuberculosis show a blood differential change with the Schilling blood differential count after 10 mgm. or less of Old Tuberculin, as evidenced by an increased degenerative shift to the left of the neutrophiles or a drop in lymphocytes.* With the major and minor premises established, our conclusions on active clinical tuberculosis are as follows: *All active cases of clinical tuberculosis show a degenerative*

shift of the neutrophilic leucocytes to the left with the Schilling blood differential count and also react to 10 mgm. or less of Old Tuberculin with a further degenerative shift of the neutrophiles to the left or a drop in lymphocytes.

Further important facts have been brought out in the analysis of the "Active Clinical" tuberculosis group: Not all increased degenerative shifts of the neutrophiles or drops in lymphocytes after tuberculin have been accompanied by a general tuberculin reaction with fever. All general tuberculin reactions with fever were accompanied by an increased degenerative shift of the neutrophiles to the left or a drop in lymphocytes. Furthermore, not all active cases of clinical tuberculosis show a general tuberculin reaction with fever after 10 mgm. of Old Tuberculin. Therefore, changes in the blood differential count following 10 mgm. or less of Old Tuberculin are more valuable than the general tuberculin reaction with fever, in detecting induced focal activity in active clinical tuberculosis.

Certainly, no methods thus far described have shown induced focal changes so constantly following tuberculin, nor measured them so accurately, as the Schilling count. This, together with the subcutaneous tuberculin test, constitute, in my experience, our most delicate and most accurate methods in the diagnosis of early manifest and induced focal activity.

POTENTIAL ACTIVITY

In the "potential-activity" group we wish to consider patients that do not show an increase in the *stabkernige* cells before tuberculin and who react with a general tuberculin reaction with fever. We also wish to consider in this group cases that have an infectious blood picture as evidenced by an increase in the *stabkernige* cells that may be due to some infection other than tuberculosis, yet in which we have a general tuberculin reaction with fever. In this series of twenty-two, we have 19 incipient, one moderately advanced, and 2 advanced cases. All but one received 10 mgm. of tuberculin as the initial dose. No serious reactions were observed, and the blood differential returned to pretuberculin findings in all instances in seventy-two hours or less. In this series of 22 cases, there were 3 patients who had an increase in *stabkernige* cells, which at the time the tuberculin test was made was questionably due to tuberculous infection. One of these patients had a laryngeal lesion which proved later to be definitely tuberculous. The second patient had advanced pulmonary tuberculosis and was working. She later

developed an infectious blood picture, and the possibility of some other infection as the cause of the blood picture was considered. On repeated examinations over a long time, the blood picture remained unaltered and

TABLE 1

A	ACTIVE CLINICAL TUBERCULOSIS				POTENTIALLY ACTIVE TUBERCULOSIS				APPARENTLY HEALED TUBERCULOSIS			
	Before tuberculin		After tuberculin		Before tuberculin		After tuberculin		Before tuberculin		After tuberculin	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Lymphocyte rise	29	70.7	0	0	15	68.2	0	0	26	76.5	0	0
Lymphocyte fall	5	12.2	36	87.8	2	9.1	19	86.4	3	8.8	32	94.1
Lymphocytes normal	7	17.1	5	12.2	5	22.7	3	13.6	5	14.7	2	5.9
Monocyte rise	17	41.2	20	48.8	2	9.1	11	50	10	29.4	11	32.4
Monocytes normal	24	58.5	21	51.2	20	90.9	11	50	24	70.6	23	67.6
Monocytic lymphocytic ratio increase	8	19.5	31	75.4	1	4.5	17	77.3	3	8.8	21	61.5
Neutrophilic degenerative shift	41	100	39	95.1	3	13.6	21	95.5	12	35.3	23	67.6
Nuclear shift index	41	100	37	90.2	10	45.5	21	95.5	20	58.8	23	67.6
Total	41		41		22		22		34		34	

Individual leucocytic reactions—and in combination. After tuberculin.

B	NEUTROPHILE SHIFT		LYMPHOCYTE FALL		MONOCYTE RISE		NEUTROPHILE LYMPHOCYTE REACTION		NEUTROPHILE LYMPHOCYTE MONOCYTE		NEUTROPHILE MONOCYTE REACTION		LYMPHOCYTE MONOCYTE REACTION		TOTAL
	Total	Per cent	Total	Per cent	Total	Per cent	Total	Per cent	Total	Per cent	Total	Per cent	Total	Per cent	
Active clinical tuberculosis	3	7.3	1	2.4	0	0	17	41.5	17	41.5	2	4.8	1	2.4	41
Potentially active	0	0	0	0	0	0	11	50	7	31.8	3	13.6	1	4.5	22
Apparently healed	1	2.9	6	17.6	0	0	16	47.1	5	14.7	1	2.9	5	14.7	34
Total	4	4.1	7	7.2	0	0	44	45.4	29	29.9	6	6.2	7	7.2	97

clinical observations established the fact that she had active clinical pulmonary tuberculosis. The third case was a patient showing enlarged cervical lymph nodes, possibly of tuberculous origin, who had a slight tonsillar infection at the time the tuberculin test was done. It was

thought possible that the tonsillar infection might be the cause of the enlarged lymph nodes. However, the tonsillar infection was very sluggish in returning to normal, but finally subsided, while the blood picture remained positive. A lymph node was removed later for biopsy and proved to be tuberculous. Therefore, all 3 cases in this series with an increased number of *stabkernige* cells proved to be active clinical tuberculosis, and the persistent infectious blood pictures were definitely of tuberculous origin.

Five other cases in this series were of special interest. They had marked loss of weight and also fatigue symptoms, with parenchymatous X-ray changes but no râles. They all had a very slight rise in temperature. Two at the time of their tuberculin tests and examinations had other members of the family suffering from active pulmonary tuberculosis. Another of these 5 cases had a questionable general reaction. The temperature did not rise a full degree, but the patient had some general symptoms which were interpreted as being due to the tuberculin. In the 3 remaining cases of this series of five, there was no family history of tuberculosis and no contact history. Because of their fever, their slight parenchymatous X-ray changes, and their marked loss of weight, they were all put on a definite tuberculosis regimen, but without complete bed-rest. All five have had remarkable improvement and have been free from symptoms and fever, with normal weight, for over two years.

Among the 14 remaining cases we have the following very interesting histories: Six were diagnosed and treated for pulmonary tuberculosis in sanatoria whose reputations are beyond question. Two had haemoptysis with parenchymatous X-ray changes and râles in the upper lobes. One of the six cases had a dry pleurisy, without any acute respiratory infection that might have been responsible for the pleurisy. Another had a spontaneous pneumothorax. A third had been treated for several years for posterior displacement of the uterus, and was found to have tuberculosis of the spine. A fourth had tuberculous lymph nodes as shown by biopsy. A fifth was one of moderately advanced disease who had been previously treated for pulmonary tuberculosis by myself. The last was an incipient case with family history of father and brother having been treated for pulmonary tuberculosis. She was markedly underweight. This patient has never taken any special care of herself, leads a rather sedentary life, and shows no particular change after four years of observation.

From the history and general tuberculin reaction and fever, the six

cases do not differ from the active cases except perhaps in the degree of symptoms. From the study of their blood before tuberculin, they do not show a degenerative neutrophilic shift as often as those in the active-clinical group. It is true that one may have difficulty at times in determining whether or not the increased neutrophilic degenerative shift is due to tuberculosis at the time. Only clinical observation can determine this point. The nuclear-shift index is much higher in this particular group than the neturophilic degenerative shift alone. The rise in the monocytes is also not as marked as in the active-clinical group, and a subnormal lymphocyte count is less common than in the active-clinical group. The monocytes were normal in a much higher percentage of cases. The monocytic-lymphocytic ratio increase was less frequent. However, when one examines the figures in table 1 (A) following tuberculin, they approximate so closely the active clinical group that there is no distinction possible.

There can be no question as to their blood reactions following tuberculin, and in this respect they are the same as the active clinical group. The neutrophiles, lymphocytes, and monocytes react identically after tuberculin as do the active-clinical cases. The detection of induced focal reactions, as measured by the Schilling count following tuberculin, is so identical that the burden of proof would be upon one who felt that the general tuberculin reaction was not of clinical importance. Prolonged observations of patients over several years, together with their histories, convince me that the general tuberculin reaction is of the greatest importance. We cannot consider such individuals as safe from further activity. My studies on these cases with the Schilling count following tuberculin only emphasize my conviction in this matter. In this respect I differ from those who think that the general tuberculin reaction in itself without any further findings is of little clinical importance. As a matter of fact, an analysis of the follow-up record reported by some observers clearly demonstrates that most of the cases that developed active disease later, in their series, came from this group of so called nonclinical reactors. Other observers have reported that the nonclinical-reactor group has fared as badly and, in some instances, worse than the clinical reactors. Certainly, from the blood studies the two groups should behave quite similarly.

It is not good policy to discharge a patient with a general tuberculin reaction as one even relatively safe from future active tuberculosis. The number of cases that develop active disease later depends on the

appreciation that the physician himself has of the value of the general tuberculin reaction, the amount of care that he will instil into his patients concerning their future activity, as well as the coöperation that patients give the physician in carrying out a program. Certainly, statistical reports, admitting that over 10 per cent of their nonclinical reactors develop active disease in the future, speak very strongly for the nonclinical reactor as a real factor in early diagnosis and tuberculosis control. To ignore this group speaks very poorly for medical supervision of suspects and is an indication of weakness in the methods of early diagnosis as well as tuberculosis control. Our former methods for detecting focal changes cannot be considered very adequate when we see the results of the Schilling count after tuberculin. As long as we expect to detect focal and induced focal changes by such crude methods as physical examination and X-ray we can never appreciate the full value of tuberculin in diagnosis. We have a method in the Schilling count which will determine such induced focal changes, and it is hoped that it will become a more universal procedure. The value of the subcutaneous tuberculin test cannot be properly estimated unless one employs methods that accurately measure focal effects of tuberculin. Focal activity is closely related to tuberculin tolerance and we must revise our ideas on what constitutes tuberculous activity.

Our conclusion in the "Active-Clinical Tuberculosis" group will serve as our major premise in the "Potential-Activity" group, namely: *all active cases of clinical tuberculosis show a degenerative shift of the neutrophilic leucocytes to the left with the Schilling blood differential count and also react to 10 mgm. or less of Old Tuberculin with a further degenerative shift of the neutrophiles to the left or a drop in lymphocytes.* In the "Potential-Activity" group we have established our minor premise, namely: *not all general tuberculin reactions show a degenerative shift of the neutrophilic leucocytes to the left with the Schilling blood differential count before tuberculin. Therefore, not all positive general tuberculin reactors have active clinical tuberculosis.* We have classified these cases, therefore, as potentially active because following tuberculin the blood reacts identically the same as in the definitely "Active-Clinical" group. The "Potential-Activity" group verified the conclusions drawn in the "Active-Clinical" group, namely: All general tuberculin reactions with fever were accompanied by an increased degenerative shift to the left of the neutrophiles or a drop in lymphocytes. Not all cases showing a degenerative neutrophilic shift to the left in the Schilling differential count or a

drop in lymphocytes after 10 mgm. or less of Old Tuberculin have a degenerative shift of the neutrophiles to the left before tuberculin. Therefore, not all cases showing a degenerative neutrophilic shift to the left in the Schilling count or a drop in lymphocytes after 10 mgm. or less of Old Tuberculin have active clinical tuberculosis.

APPARENTLY HEALED

We wish to consider here cases that have had definite changes in the Schilling count following tuberculin, but have had no fever reaction and no general tuberculin reaction. In this group of thirty-four there were 4 advanced, 7 moderately advanced, and 23 incipient cases. All but five received 10 mgm. or less of Old Tuberculin as the initial dose. No serious reactions were observed, and the differential count returned to the pretuberculin findings in seventy-two hours or less with the exception of two or three cases, and these returned to normal within five days. Twelve in this series of thirty-four showed a degenerative neutrophilic shift with the Schilling method, as evidenced by an increase in the number of the *stabkernige* cells. At the time the tuberculin test was done it was impossible to state whether the blood picture with the increased number of *stabkernige* cells was due to tuberculosis or some other infection. Obviously, clinical observation alone could determine this point. The infectious blood picture was proved definitely to be due to tuberculosis in eleven of the 12 cases after a few weeks' observation.

In one of the cases, it was only after several months that any definite conclusions could be drawn as to the cause of the infectious blood picture. All methods of investigation failed to show that there was any nontuberculous infection responsible for the increased number of *stabkernige* cells. Six years previously this patient had been diagnosed as having active clinical pulmonary tuberculosis and was running a slight elevation of temperature which still persisted for at least six months after the tuberculin test was made. The final conclusion was that the patient had been suffering from a low-grade active tuberculous infection and his clinical course improved when he was put on a proper regimen.

All 12 cases with an increased number of *stabkernige* cells after observation proved definitely active clinical cases of tuberculosis. Two of them were lymph-node cases in addition to having pulmonary lesions. This leaves us with twenty-two that showed no increase in the number of *stabkernige* cells. After prolonged clinical observation, none of these was shown to have active clinical disease. It is interesting to note, how-

ever, that nine of the twenty-two had been previously treated for active clinical pulmonary tuberculosis by myself or by other physicians whose ability could not be questioned. Nine other patients had active cases of clinical tuberculosis in the family to my personal knowledge at the time the examinations were made. In one other case the patient had a pleurisy unexplained by any other cause than tuberculosis. In another case of moderately advanced disease, the patient was markedly underweight, and history, X-ray, and physical examination would lead one to suspect that this patient had had active clinical disease previously.

This leaves us with two in which the past history and contact history could not give us anything definite in the way of exposure to the disease or previous symptoms of activity. Both of these were markedly under weight and complained of considerable fatigue, and had fever. One had a chronic sinus infection. This latter patient was referred to me for examination because the nose-and-throat specialist could not explain her symptoms as due to sinusitis alone. Both have improved remarkably on a proper regimen.

Certainly, from a clinical standpoint, the 34 cases check remarkably well with either definite evidence of active clinical tuberculosis previously, or definite history of exposure, with the exception of two. These two are still under observation, and up to this time they have not developed definite changes in physical signs or X-ray. One advanced case in this group died twenty-three months later of pulmonary tuberculosis. She could not be convinced of the necessity of taking proper care of herself, and doubted the diagnosis of unhealed tuberculosis.

Before tuberculin, the blood differentials in this series of "Apparently-Healed" cases showed a higher percentage of lymphocytic rise than the potential and active groups. The monocytes on the other hand were perhaps higher than in the potentially active group because of the number later proved to be active. The same thing holds true for the neutrophilic degenerative shift and the nuclear-shift index. It is interesting, also, to note that the nuclear-shift index was higher than the neutrophilic degenerative shift, just as in the "Potential-Activity" group. The monocytic rise, as well as the increase in the monocytic-lymphocytic ratio, was less frequent than the changes in the neutrophiles and lymphocytes. Throughout these groups of "Active," "Potentially-Active," and "Apparently-Healed" cases, the monocytes were found to react less frequently than either the neutrophiles or the lymphocytes. The variations are seen in table 1 (A).

The reactions in the differential count following tuberculin in the apparently-healed group show a very striking difference from the active and potentially-active groups. There is decidedly less reaction among the neutrophiles, as evidenced by a much smaller percentage of neutrophilic degenerative shift as well as less change in the nuclear-shift index. In the active and potentially-active cases, there is an increase in the number of *stabkernige* cells following tuberculin in 95.5 per cent of the cases, whereas in the apparently-healed group there is an increase following tuberculin in only 67.6 per cent. The lymphocytes on the other hand show a larger drop in the apparently-healed cases than do the active and potentially-active ones. The monocytes, on the other hand, show a lower percentage of rise following tuberculin in the apparently-healed group than in the active and potentially-active groups. Table 1 (A) shows these changes.

In table 1 (B) it is interesting to note the relatively large number of cases showing a drop in lymphocytes alone, without other change following tuberculin. It is also interesting to observe the number of cases showing a lymphocytic and a monocytic drop without other change. A further striking observation in table 1 (B) is the absence of a case showing only a monocytic rise. The value of the neutrophiles and lymphocytes is obvious. These show a change after tuberculin in every case, either alone or in combination. In a previous article I pointed out that if one used graded doses of tuberculin one could first observe a drop in the lymphocytes, and then a rise in the *stabkernige* cells. The increase in the *stabkernige* cells, as pointed out, followed very closely upon the drop in lymphocytes. These reactions occurred before the general tuberculin and fever reactions. Table 1 (B) shows the individual blood changes found in 97 cases reacting to tuberculin. The lymphocytes reacted with a drop in 89.7 per cent, the neutrophiles in 85.6 per cent, and the monocytes in 43.3 per cent. In combination, the lymphocytes and neutrophiles reacted in 100 per cent of the cases. The monocytes have been far less regular in their behavior before as well as after tuberculin.

It is extremely interesting to note among the apparently healed that twelve proved definitely to be active clinical cases of tuberculosis. In the definitely active group we had seven who failed to react with fever and a general tuberculin reaction, and in this series 12 additional cases. This is a definite answer to the problem that the fever and general tuberculin reaction are very unreliable methods to judge the value of the subcutaneous tuberculin test. Focal reactions, as evidenced by localized

symptoms, physical signs, and X-ray examinations, are equally unreliable. The Schilling count demonstrates these facts very conclusively and gives us at least the hope of a solution of the problem. In every instance, the differential blood count shows unmistakable changes in these cases, regardless of fever or general tuberculin reaction.

This series, furthermore, has demonstrated 9 cases diagnosed as active clinical tuberculosis some years previously by men qualified as experts in tuberculosis. They show definite blood changes following tuberculin, but no fever, general or focal reaction. With the experience of the seven in the active group and the twelve in the apparently-healed group who proved to be cases of active tuberculosis, there can be little doubt as to the value of the Schilling count in the detection of the various stages of activity. The blood changes following tuberculin represent induced focal activity and, in the absence of any other findings, represent the earliest demonstrable stages of activity.

The value of the subcutaneous tuberculin test, as judged by the Schilling count, offers us a solution to the early diagnosis of activity. The fact that all active cases really react to the subcutaneous tuberculin test is an invaluable finding. Further, to be able to follow known cases sufficiently long and demonstrate that they failed to react with fever and general tuberculin reaction or focal signs, but react with the blood differential, is further unmistakable proof of the value of the subcutaneous tuberculin test.

Some of the cases showing blood differential changes after tuberculin had positive sputa for eleven years previous to the test. Some of them have not shown any of the usually accepted signs of activity for eight years. Certainly, one would be justified in classifying them with the ordinary classifications as apparently-cured cases. I have seen cases classified as apparently-healed develop activity and die of the disease. Without the blood differential count and the tuberculin test, at least twelve of the cases classified as apparently-healed would not have been recognized early and could possibly have developed further spread of the disease with further disability. This series certainly bears out the words of Krause, "Tuberculin effects on the body which we observe in practice are focal effects. Tuberculin reaction that minifests itself to us is a focal reaction. Tuberculin tolerance is focal tolerance." Furthermore, he states that "the possibility of inactivity cannot be entertained as long as constitutional symptoms are manifest or can be induced. Constitutional symptoms become therefore our best indicator and guide of activity and

it is this which may illumine the indefinite and shadowy line between the actual and potential patient."

We have had tuberculin to test focal tolerance for many years. The failure has been to use an accurate method for the detection of focal activity and induced focal activity following tuberculin. Certainly, our previous methods have had very little semblance of even remotely attempting to detect tissue changes at the site of tubercle. With the renewed interest in blood differential counts in recent years, there is some hope again of approaching the problem of tuberculous activity more accurately. Any method suggested must be practical and must lend itself to daily practice. The Schilling count meets all of these requirements. It should be looked upon as would a biopsy. It should be performed by qualified laboratory physicians, and interpreted by physicians with a haematological background. It is obvious in this series of apparently-healed cases that an increase in the *stabkernige* cells and an increase in the nuclear-shift index were not considered in themselves positive evidence of active tuberculosis. Every means was used to eliminate all types of infection as possible causes of the blood picture. To differentiate activity from potential activity and apparently-healed tuberculosis, in the presence of an infectious blood picture before tuberculin, requires clinical experience. This clinical experience must rule out all other infections as the cause of the infectious picture.

The interpretations of the blood reactions following tuberculin are not so difficult. Any tuberculous lesion that reacts with tuberculin, as evidenced by changes in the Schilling count, cannot be considered healed. It shows induced focal activity. The degree of activity depends on the changes present before tuberculin was used. Clinically, we have no satisfactory standard of activity. The diagnosis of activity is and has been largely a personal equation. What we sorely need is a definite standard and measure that can be applied by all, and to all cases, and one that brings clinical activity more closely to focal activity.

Not all cases showing a degenerative neutrophilic shift to the left in the Schilling differential count or a drop in lymphocytes after 10 mgm. or less of Old Tuberculin had a degenerative shift of the neutrophiles to the left before tuberculin. Therefore, not all cases showing a degenerative neutrophilic shift to the left in the Schilling differential count or a drop in lymphocytes after 10 mgm. or less of Old Tuberculin have active clinical tuberculosis.

HEALED TUBERCULOSIS

In the group of "Healed Tuberculosis" we wish to consider cases having a normal blood differential with the Schilling method, or cases that have a degenerative neutrophilic shift to the left of doubtful origin, and who fail to react with any blood changes following 10 mgm. of Old Tuberculin. In this group there are 208 cases failing to show blood changes in the Schilling count following 10 mgm. of Old Tuberculin. All of them, with the exception of nineteen, received 10 mgm. as their initial dose, but twenty-five failed to get even a local reaction. All of the other cases had slight to moderate and, in a few instances, severe local reactions. None had fever or a general tuberculin reaction. Many had infectious blood pictures due to infections other than tuberculosis. A detailed analysis of their individual blood pictures is not deemed necessary in this report because they showed no changes following tuberculin.

In this group of 208 cases, one hundred and forty-six were diagnosed as having incipient pulmonary tuberculosis because they showed definite parenchymatous X-ray changes. Forty-three were classified as non-tuberculous. They had no evidence of tuberculosis anywhere, except possibly a few calcified lymph nodes as evidenced by X-ray. There were 11 cases diagnosed as moderately advanced pulmonary tuberculosis on X-ray, and eight as advanced cases of pulmonary tuberculosis. Of the incipient cases, three were personally treated by me for pulmonary tuberculosis, with positive sputum, and two were treated by reputable sanatoria with a diagnosis of incipient pulmonary tuberculosis. Therefore, in this series of healed cases there are five that at one time had unmistakable evidence of active pulmonary tuberculosis and positive sputum. All five have been working for at least six years, and the longest case about eleven years, without evidence of active pulmonary tuberculosis. One has gone through her fifth pregnancy. In the "Moderately-Advanced" group there is one patient whom I treated for active pulmonary tuberculosis at one time, with a positive sputum, and who has been working for five years without any sputum or symptoms of active pulmonary tuberculosis. Another patient was treated in a reputable sanatorium, and eight years have elapsed since he had active signs. Both had positive sputum. In the "Advanced" group are 2 cases whom I personally treated for active pulmonary tuberculosis and who failed to react with 10 mgm. of tuberculin. They have been working for seven years or longer without symptoms. Both had positive sputum. Two additional

cases were treated in reputable sanatoria for active tuberculosis, one nine years ago and the other eleven years ago. Only one of the 208 cases has shown any signs of activity, and all have been under observation from two to twelve years.

There is one patient, who is of special interest in the "Healed" group, and whose history might be repeated in detail at this point because she later developed active disease and died of pulmonary tuberculosis. Without general tuberculin or blood reactions, she had only a moderately severe local reaction to 10 mgm. of Old Tuberculin.

This patient, white, female, twenty-nine, married, was examined May 16, 1930. Father died of pulmonary tuberculosis. One brother had pulmonary tuberculosis and one sister died of the disease. Patient was well nourished and showed nothing on physical examination. X-ray showed definite parenchymatous changes which were diagnosed as tuberculous. Patient took care of her brother, who had far advanced pulmonary tuberculosis, and was in intimate contact with him from June 1, 1930, to June 1, 1931, when her brother died of pulmonary tuberculosis. Patient had gained in weight from 117 to 130 lbs. from May 16, 1930, to March 1, 1931. I did not examine her after March 1, 1931. She became pregnant some time in March, 1931, and consulted a physician who took care of her pregnancy. She developed marked vomiting for the first two or three months of her pregnancy and lost considerable weight. She was diagnosed as having pulmonary tuberculosis in July, 1931. Miscarried in August, 1931, and died in December, 1931.

This case is mentioned in detail because it is the only one of the 208 cases failing to react with tuberculin who developed active clinical disease. All others who developed active disease were among those who showed definite blood changes following tuberculin. This latter case is possibly a failure, but the question of reinfection from her brother, together with pregnancy and miscarriage with marked vomiting as a factor, must be considered. At any rate, the case is reported as it is.

Among the 25 cases failing to get even a local reaction to 10 mgm. or less of tuberculin twelve were diagnosed by X-ray as having incipient pulmonary tuberculosis. Eleven showed no parenchymatous X-ray changes and were diagnosed as nontuberculous. One was a moderately advanced case, and the other an advanced case of pulmonary tuberculosis. All of this series of healed cases have been under observation for two years or longer and are all working and doing very well, with the exception of the one who died of pulmonary tuberculosis and previously mentioned in detail.

In the "Healed" series, we have established that: *Not all cases that show a degenerative neutrophilic shift to the left in the Schilling blood differential count show a further degenerative shift of the neutrophiles or a drop in lymphocytes after 10 mgm. or less of Old Tuberculin. Therefore, not all cases showing a degenerative neutrophilic shift to the left in the Schilling blood differential count have active clinical tuberculosis.* In the "Potentially-Active" group and in the "Apparently-Healed" group, we established the premise that not all cases showing a degenerative neutrophilic shift to the left in the Schilling count have active clinical tuberculosis. We also established the premise in the "Potentially-Active" and "Apparently-Healed" groups that not all cases showing a degenerative neutrophilic shift to the left or a drop in lymphocytes in the Schilling count following 10 mgm. or less of Old Tuberculin have active clinical tuberculosis. Therefore, not all cases showing a degenerative neutrophilic shift to the left in the Schilling count and a further degenerative neutrophilic shift or a drop in lymphocytes following 10 mgm. or less of Old Tuberculin have active clinical tuberculosis.

In an analysis of all of the cases in this series an increase in the number of monocytes is usually associated with activity. It may, however, be associated with healing, but usually it represents increased activity. An increase in lymphocytes is also usually associated with healing. An increase in the lymphocytes and a drop in the monocytes is usually a favorable reaction toward healing. A degenerative neutrophilic shift to the left is associated with activity. An increase in the degenerative neutrophilic shift to the left associated with a drop in lymphocytes usually means increased activity. The monocytes are quite variable, and may or may not be increased at the same time. The degree of neutrophilic shift to the left together with the degree of drop of lymphocytes is our best index of the degree of activity. There were no regenerative shifts of the neutrophiles in this series, that is, cases showing an increase in "juveniles," because such cases are usually not suitable for tuberculin diagnosis and are too sick. Neither were there any cases in this series showing an extreme regenerative picture with myelocytes.

The diagnosis of active clinical tuberculosis cannot be made from the Schilling differential alone. However, a normal Schilling count excludes definitely active tuberculosis. If we have a positive degenerative neutrophilic shift in the Schilling count and a further change with an increased degenerative neutrophilic shift or a drop in the lymphocytes following 10 mgm. or less of tuberculin, we have the two requisites for a

diagnosis of active tuberculosis. If we can eliminate all other infections as the cause of the blood picture we have a right to make a diagnosis of active tuberculosis. If the patient has a positive infectious blood picture due to tuberculosis, as determined by clinical observation, we have a right to make a diagnosis of active clinical tuberculosis. Clinical observation must determine whether the blood picture before tuberculin can be explained on any other basis than tuberculosis. Clinical opinion can only be expressed in favor of tuberculosis in a doubtful case, if we have a positive blood reaction following tuberculin. Neither the blood alone, nor the blood changes after tuberculin alone, nor clinical opinion alone, can settle the question of active tuberculous infection satisfactorily. It is only by the combination of all three that we can establish the diagnosis of active clinical tuberculosis in doubtful cases. The best and simplest measure for the detection of active tuberculous infection is

TABLE 2

TYPES OF POSITIVE TUBERCULIN REACTION			NEGATIVE BLOOD REACTORS		
	Number	Per cent		Number	Per cent
Local	280	91.9	Nontuberculous	43	20.7
General	56	16.4	Incipient	146	70.2
Focal	15	4.9	Moderately advanced	11	5.3
Schilling blood differential	97	31.8	Advanced	8	3.8
Total	280	91.9	Total	208	68.2

the Schilling blood differential count. The best and simplest method to measure induced focal tuberculin reactions is the Schilling count. Therefore, the Schilling count, together with the subcutaneous tuberculin test, constitute our most delicate and most accurate methods in the diagnosis of early manifest and induced focal activity. With the diagnosis of tuberculosis established, the Schilling count becomes our most reliable guide in determining the progress of the disease.

PROGNOSIS

The prognosis of tuberculosis with the blood differential count alone is not without its very decided limitations. Much has been written about the value of the Schilling differential and other methods in the prognosis of tuberculosis. One can measure the degree of activity very accurately as well as the favorable reactions toward healing. However, the prognosis of tuberculosis, unfortunately, is related to a great many

mechanical factors. These mechanical factors are beyond the power and scope of any blood differential count to forecast. Rupture of a tuberculous abscess may very suddenly and very seriously alter the entire clinical picture. No one can forecast when or where an abscess may rupture, and it is impossible therefore to forecast such serious complications as tuberculous meningitis, tuberculous bronchopneumonia, or fatal haemoptysis. No one can measure with the blood differential count the myocardial changes that are going on, while the blood count shows only a moderately severe infection. Cardiac failure, associated with dyspnoea, cyanosis and oedema, is fatal in most patients with only a moderately severe blood picture. The prognosis of tuberculosis, therefore, cannot be measured by the blood differential count alone. Many false impressions have been given as to the prognostic value of the various cells and forms of blood differential counts.

TABLE 3

	NUMBER OF CASES		ACTIVITY DURING PERIOD OF OBSERVATION		ACTIVITY AT PRESENT		WORKING 1–5 YEARS OR LONGER. NO ACTIVITY		DIED	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Active clinical tuberculosis..	41	13.4	41	100	4	9.7	36	87.8	1	2.4
Potentially active.....	22	7.2	3	13.6	2	9.9	20	90.1	0	0
Apparently healed.....	34	11.1	12	35.3	2	5.9	31	91.2	1	2.9
Healed.....	208	68.2	1	0.48	0	0	207	99.12	1	0.48
Total.....	305	100	57	18.7	8	2.6	294	96.4	3	0.98

It is true that a rise in lymphocytes associated with a decrease in the degenerative neutrophilic shift portends a favorable prognosis. It is also true that a rise in lymphocytes and a drop in monocytes is usually a favorable reaction. An increase in the neutrophilic degenerative shift to the left is often associated with a drop in lymphocytes and is of unfavorable prognosis. The eosinophiles and basophiles are too variable to place much significance in them in an individual case. With the diagnosis of tuberculosis established, there is no better method of following the course of the patient's progress than by a Schilling count.

CLASSIFICATION

As a result of these studies, the classification of activity and healing was suggested in a previous article in the AMERICAN REVIEW OF TUBER-

CULOSIS in 1929. The classification is based on the Schilling count and the subcutaneous tuberculin test:

Active Tuberculosis: A patient who has a degenerative neutrophilic shift to the left with the Schilling blood differential, due to tuberculous infection, with a further shift to the left of the neutrophilic leucocytes or a drop in the lymphocytes following 10 mgm. or less of Old Tuberculin.

Potentially Active Tuberculosis: A patient who has a normal or a degenerative neutrophilic shift in the Schilling differential, of doubtful origin, and who has an increased degenerative neutrophilic shift or a drop in lymphocytes following 10 mgm. or less of Old Tuberculin. This is associated with a general tuberculin reaction with fever.

Apparently Healed: A patient who has a normal or a degenerative neutrophilic shift in the Schilling blood differential, of doubtful origin, and who has an increased degenerative neutrophilic shift or a drop in lymphocytes following 10 mgm. or less of Old Tuberculin, not associated with a general tuberculin reaction with fever.

Healed Tuberculosis: A patient who has a normal or degenerative neutrophilic shift to the left in the Schilling blood differential of doubtful origin, and who fails to get any change in the Schilling blood differential following 10 mgm. of Old Tuberculin.

CONCLUSIONS

1. The interpretation of the clinical importance of the subcutaneous tuberculin test can best be judged by the Schilling blood differential count.

2. The Schilling count is a more accurate measure of induced focal reactions than are fever, general tuberculin reactions, physical signs, or X-ray.

3. A classification of the various stages of activity as well as those of healing can best be made by the Schilling count together with the subcutaneous tuberculin test.

4. The subcutaneous tuberculin test together with the Schilling count is our most delicate and most accurate method in the diagnosis of early manifest and induced focal activity.

THE EFFECT OF TUBERCULIN ON SPERMATOZOA FROM NORMAL AND TUBERCULOUS GUINEA PIGS[1]

LILIAN C. DONALDSON AND ARTHUR J. VORWALD

In 1924 this laboratory (1) published experiments showing that the germinal epithelium of tuberculous male guinea pigs is very sensitive to tuberculin, whereas the germinal epithelium of normal animals is not affected. It was further noted that in fixed tissues, in the tubular degeneration, which follows within 24 hours after the intratesticular tuberculin injection, it is the spermatocytes and spermatids which suffer most markedly, while the spermatozoa and spermatogonia are not greatly affected at first. It would appear, then, that the spermatozoa in the tuberculous animal are less highly sensitized to tuberculin than are germ cells in earlier stages of maturation. With these points in mind, it seemed of interest to determine whether any hypersensitiveness to tuberculin could be demonstrated in the spermatozoa of tuberculous animals. Should the results be positive, a very simple tuberculin test might then be devised which would greatly reduce the number of guinea pigs needed to ascertain the potency of various tuberculins.

Guinea pigs, weighing approximately 500 gm., were each given an injection of 0.2 mgm. of live tubercle bacilli (H 119, a strain of human type bacilli of moderate virulence) into the left axilla. Approximately 5 weeks later in each case, spermatozoa were collected by the ejaculation method of Moore (2), and gently shaken in 25 cc. of fresh Locke's solution which had previously been adjusted to a known pH, using the potentiometer method. These spermatozoa were then added to varying dilutions of tuberculin or tuberculin fractions in Locke's solution, and their motility at room temperature observed microscopically, and compared with that of spermatozoa from normal animals subjected to identical conditions. Following each experiment the animals were tested for cutaneous reaction to tuberculin, or in some instances to a tuberculin protein fraction, and then autopsied. The tests were done to make certain that the tuberculous animals, and those only, were properly sensitive; and they were done

[1] From the Department of Pathology of the University of Chicago, Chicago, Illinois.

after the collection of the spermatozoa, rather than before, in order to avoid influencing that sensitiveness in any way.

Preliminary experiments showed (1) that the motility of guinea-pig spermatozoa was more marked and better sustained in both Locke's solution and tuberculin dilutions in Locke's when the solutions gave a slightly alkaline reaction, a result which was to be expected from the work of others (3), and (2) that only in very strong concentrations of tuberculin were any effects upon motility noticeable. Any possible effect of dilutions of tuberculin in Locke's, even of 1:1000 or 1:100, were masked by the gradual general decrease in motility of spermatozoa from both normal and tuberculous animals, even in pure Locke's solution over the period of 7 to 8 hours usually covered by a given experiment, and by the roughness of the method of gauging motility (4).

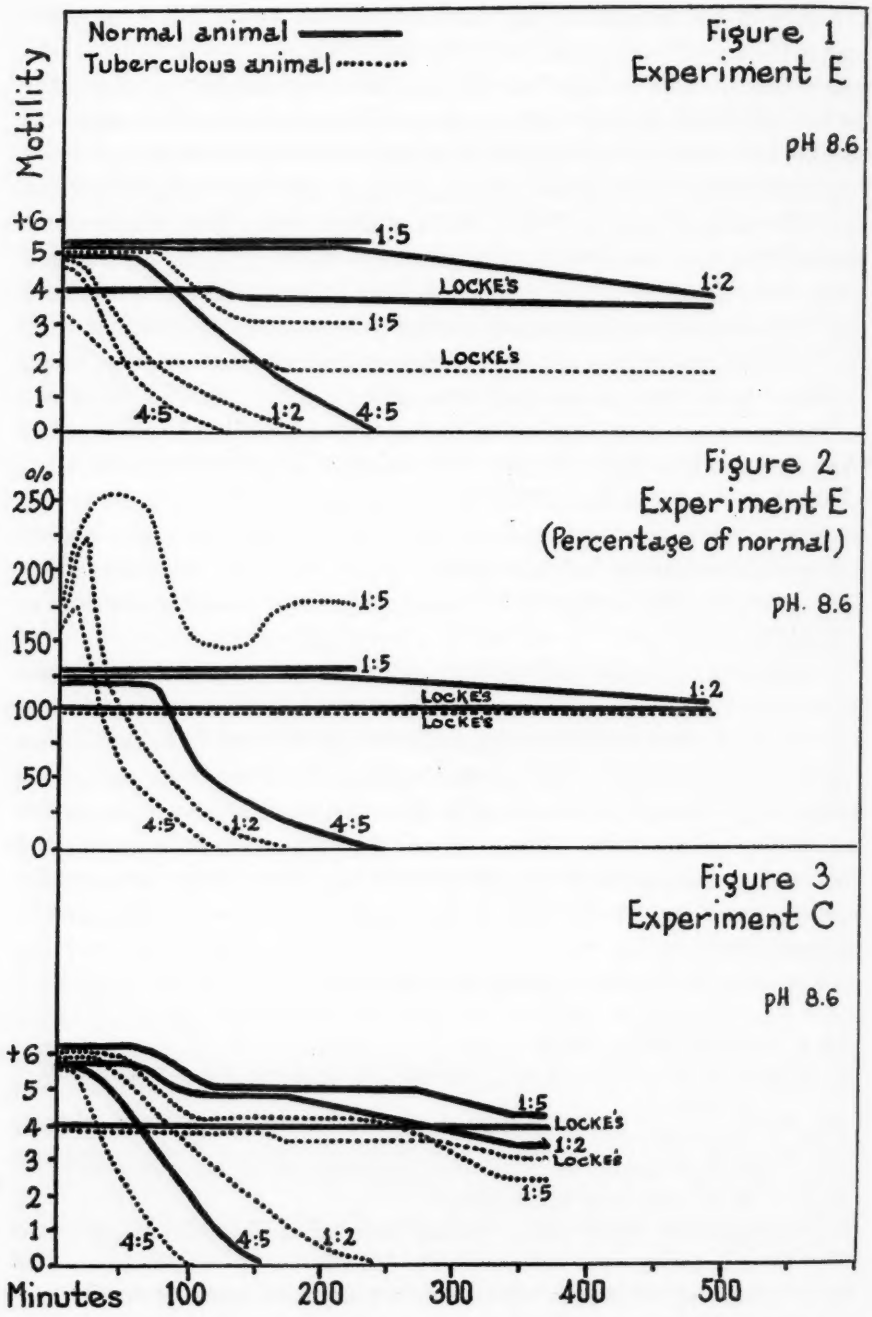
Seven experiments, including in each case a normal and a tuberculous guinea pig, were then run, using dilutions of tuberculin in Locke's solution of 4:5, 1:2, 1:5, and 1:10 in each case. These are very strong solutions, the osmotic pressures of which are far from physiological. This fact need not invalidate the experiments, however, since spermatozoa from both sensitized and nonsensitized animals were in each case subjected to identical solutions. In two instances the substance used was *SOT*, tuberculin made on Long's synthetic medium (5), but otherwise prepared as Koch's Old Tuberculin; in the other five experiments freshly prepared *SMT*, Long's synthetic medium tuberculin, was used. No appreciable difference was noted in the results with the two tuberculins. In plain Locke's solution the motility of the spermatozoa from both normal and tuberculous animals showed only a slight diminution over a period of 7 to 8 hours, the decrease usually being greater in the case of the spermatozoa from the tuberculous animals. Usually, too, the original level of motility in Locke's was less in the latter group than in the corresponding normal. In the tuberculin dilutions the motility of spermatozoa from both the normal and tuberculous animals was accelerated during the first minutes of observation. In dilutions of 4:5 the motility decreased sharply, ceasing entirely within 30 (experiment C) to 115 minutes (experiment E) in the case of spermatozoa of the tuberculous animals, and in 60 (experiment C) to 225 minutes (experiment E) in that of normal animals, the loss of motility in any given experiment always occurring first in the spermatozoa from the tuberculous animal, either in this dilution or others cited. In dilutions of 1:2 the motility ceased in 75 to 235 minutes for the tuberculous animals, while for the corresponding normals

it ceased in 120 minutes in the shortest instance, and in the longest instance the motility was still 3+ at the end of 8 hours of observation. It is here that the widest difference was noted between the effect of tuberculin on the spermatozoa from the normal and from the tuberculous animals. In dilutions of 1:5 the motility of spermatozoa from tuberculous animals was at the close of the experiments usually just below that of spermatozoa from the same animals in plain Locke's solution, while those from normal animals had just lost their initial acceleration and were at about the same level as those of the corresponding normal control in Locke's solution. Spermatozoa from both the tuberculous and the noninfected groups showed in 1:10 dilutions a perhaps slightly less-marked original acceleration of motility, which was maintained throughout most of the period of observation, only toward the end of the experiments falling to the level of the corresponding tuberculous or normal control in plain Locke's solution. The pH at the beginning of the various experiments varied between 8.2 and 8.6. The tuberculous animals gave positive skin reactions, and at autopsy showed good caseous axillary nodes, with but little other gross tuberculosis. The noninfected animals gave no cutaneous reaction to tuberculin.

Figure 1 is a graphic representation of typical results, those obtained in experiment E. It will be noted that, though the motility of the spermatozoa from the tuberculous animal reaches zero in each dilution somewhat before that of the normal animal, the tuberculous control in plain Locke's solution is less motile than the spermatozoa from normal animals, as pointed out above. It should be mentioned here that the tuberculous animals were usually slightly less heavy than the normals, and appeared feebler, an observation applicable to the animals used in experiment E.

A key to the motility readings is as follows:

+6 = whirling madly, racing.
+5 = progression very rapid in practically all instances, and a rolling motion present.
+4 = rapid progression in most instances.
+3 = fair progression in many instances; a number of spermatozoa nonmotile, or showing only tail motion.
+2 = progression in only a few; in many cases tail motion only, clumps; some nonmotile.
+1 = stationary, clumped; tail motion in many, and many nonmotile.
0 = completely nonmotile.



FIGS. 1, 2 AND 3. COMPARISON OF THE EFFECT OF VARYING DILUTIONS OF TUBERCULIN ON THE MOTILITY OF SPERMATOZOA FROM NORMAL AND TUBERCULOUS ANIMALS

Figure 2 shows the results of the same experiment charted in "percentage of normal," taking the motility of spermatozoa from the normal animal at any given instant as 100 per cent in Locke's solution, and showing the percentage variations from the base-line resulting when such spermatozoa were in varying dilutions of tuberculin. The motility level in plain Locke's solution of the spermatozoa from the tuberculous animals was also expressed as 100 per cent at any given moment, and the variations caused by the tuberculin dilutions charted against that level. This was done in an effort to clarify the results by eliminating as nearly as possible the factor of general lower motility of spermatozoa from the tuberculous animal in the control solution.

For the same reason figure 3 is included, showing the results obtained in experiment C, in which the spermatozoa from both normal and tuberculous animals continued to show the same degree of motility throughout most of the experiment. It will be noted that there is here again a distinct difference between the motility of spermatozoa from the tuberculous animal in a 1:2 dilution of tuberculin in Locke's solution, and that of those from the uninfected animal, an effect which cannot this time be so readily accounted for without reference to hypersensitiveness, since difference in the motility levels in plain Locke's solution is in this case practically nonexistent.

While in general this group of 7 experiments, together with the preliminary group, had failed to show any distinct hypersensitiveness of spermatozoa from tuberculous animals to concentrations of tuberculin of any strength (4:5 to 1:1000 of *SOT* and *SMT*), it was not certain that the feebler motility in general of spermatozoa from tuberculous animals, as shown by their motility curves in Locke's solution, would account for all of such minor differences as were noted between the normal and tuberculous groups in the tuberculin dilutions. An experiment was therefore planned in which the effect of synthetic-medium tuberculin was to be compared with that of the synthetic medium on which it was made, and of purified fractions of tuberculin protein and carbohydrate, for the purpose of showing which fractions caused the increase and sharp decreases in motility noted above, and if such fraction or fractions had a greater effect on the motility of spermatozoa from the tuberculous animals than on those from the normal. An acid-fast timothy-bacillus protein was also used as an example of a relatively nontoxic protein derived from an acid-fast organism. At the same time dilutions of diphtheria toxin were prepared, for the purpose of determining whether spermatozoa from

tuberculous animals were more susceptible to any toxin than those from uninfected animals.

The tuberculin protein fractions (6), *TPA* (tuberculin protein, ammonium sulphate precipitated, purified) and *TPU* (tuberculin protein ultrafiltered), together with a carbohydrate fraction from tuberculin, and the timothy-bacillus protein as well, were given by Dr. Florence B. Seibert, who also supplied the following analyses on their dry weights.

Fraction	*Per cent nitrogen*	*Per cent polysaccharide*
TPA	16.2	2.8
TPU	4.9	37.6
Carbohydrate (7)	0.1	55.0
Timothy-bacillus protein (7)	13.5	6.9

In searching for the strength of solution that would be necessary to produce an effect on motility, a preliminary experiment was performed, using spermatozoa from two tuberculous and one normal animal, and subjecting them both to plain Locke's solution as a control and to dilutions containing from 0.0006 to 0.5 mgm. of *TPA* per cc. of Locke's solution. These dilutions were chosen as having within their range amounts of *TPA* comparable to those giving maximum cutaneous reactions (6). The results of the experiment were entirely negative. The spermatozoa from the tuberculous animals maintained a 3+ motility throughout the experiment (3 hours), both in plain Locke's and in the *TPA* dilutions, and the spermatozoa from the uninfected animal showed a 4+ motility in all dilutions. At the close of the experiment 0.2 cc. of normal saline solution, containing a total of 0.125 mgm. of *TPA*, was injected intracutaneously into each of the 3 animals. At the end of 24 hours the two tuberculous animals gave a good positive skin reaction, as evidenced by hyperaemia and induration, while the normal animal was negative in reaction.

It was therefore decided to use very strong dilutions of the tuberculin fractions in the final experiment, and to have the amounts bear some relation to the minimum lethal dose for an adult guinea pig. In 5 cc. (the final volume of any finished suspension of spermatozoa) of a 4:5 dilution of synthetic tuberculin, there was estimated to be 4 times the minimum lethal dose for an adult guinea pig. The effect of the synthetic medium was compared in dilutions of 4:5 and 1:2 with corresponding dilutions of synthetic tuberculin. The *TPA* fraction was dissolved in Locke's solution in such amount that 5 cc. contained, after addition of the spermatozoa, 4 times the minimum lethal dose for an adult guinea pig (8),

or 5 mgm. per cc. The carbohydrate fraction was also used in a dilution containing 5 mgm. per cc. The *TPU* fraction was used in such weight that the finished 5 cc. of spermatozoa suspension contained per cc. an amount of nitrogen approximately equal to that per cc. in the *TPA* solutions, according to the analyses given above, that is, 20 mgm. of *TPU* per cc. The solution of timothy-bacillus protein also contained 20 mgm. per cc. (the original idea being to compare the effect of similar concentrations, using a toxic (*TPU*) and a nontoxic (timothy) protein fraction). The diphtheria toxin was prepared in three strengths, one solution containing 4 times the minimum lethal dose for an adult guinea pig in 5 cc. of solution, the second the minimum lethal dose, and the third one-tenth the minimum lethal dose. Due to the small quantities of material available in some instances, it was possible to adjust the pH only very roughly before addition of the spermatozoa, but potentiometer readings were made immediately at the close of the experiment and are recorded in figure 4.

The experiment was done on two sets of animals, *J* and *K*, both in excellent condition, with almost identical results. Those obtained in experiment K are given in figure 4. The time of observation in this case was only $4\frac{1}{2}$ hours. It will be seen that for any given dilution the motility curves given by spermatozoa from the normal and the tuberculous animal were practically superimposed; there was not the least indication of hypersensitiveness even in the very strong solution of the purified and very potent tuberculin protein, *TPA*. In Locke's solution the curves showed the usual slight gradual diminution of motility. Synthetic-medium tuberculin, in dilutions of 4:5 and 1:2, caused an initial acceleration of motility, followed by the sharp decrease and cessation seen previously. The synthetic medium, 4:5 and 1:2, caused a like acceleration and a similar, though less rapid, diminution of motility. *TPA* not only completely failed to demonstrate any hypersensitiveness in the spermatozoa from the tuberculous animal, but caused neither acceleration nor diminution of motility over that manifested in Locke's solution; instead, the motility curves were in both instances maintained at their original level, if anything for a slightly longer period than in Locke's. On the other hand, a similar concentration of the carbohydrate fraction, which has been shown to be nontoxic to tuberculous guinea pigs even when as much as 50 mgm. are injected intraperitoneally (6), caused a prompt cessation of motility in spermatozoa from both infected and noninfected animals. The curve given by the *TPU* solution, whose nitrogen content

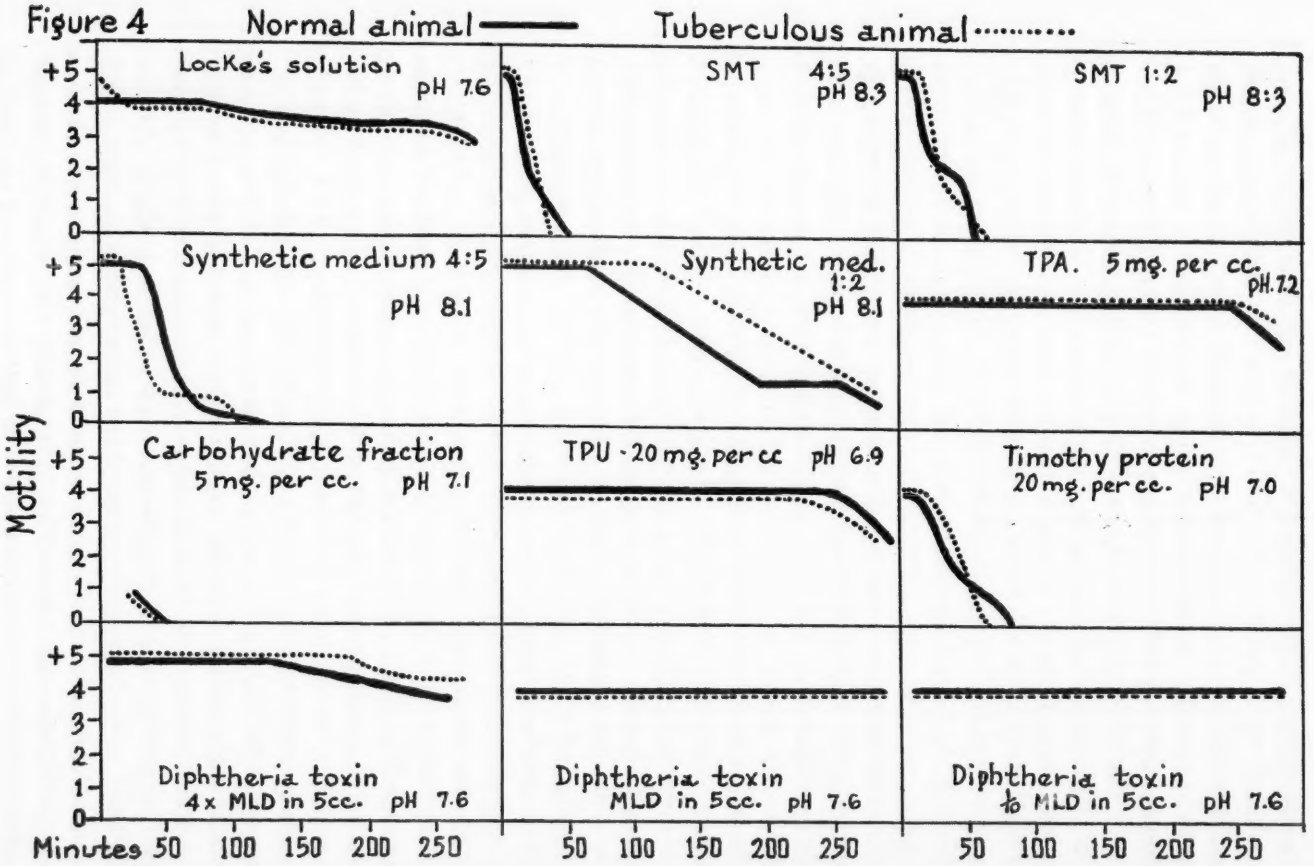


Figure 4
Normal animal
Tuberculous animal
Locke's solution pH 7.6
SMT 4:5 pH 8.3
SMT 1:2 pH 8:3
Synthetic medium 4:5 pH 8.1
Synthetic med. 1:2 pH 8.1
TPA. 5 mg. per cc. pH. 7.2
Carbohydrate fraction 5 mg. per cc. pH 7.1
TPU - 20 mg. per cc pH 6.9
Timothy protein 20 mg. per cc. pH 7.0
Diphtheria toxin 4 x MLD in 5cc. pH 7.6
Diphtheria toxin MLD in 5cc. pH 7.6
Diphtheria toxin 1/10 MLD in 5cc. pH 7.6
Motility
+5
4
3
2
1
0
Minutes 50 100 150 200 250

FIG. 4. COMPARISON OF THE EFFECT OF DILUTIONS OF TUBERCULIN, SYNTHETIC-MEDIUM, TUBERCULIN-PROTEIN AND CARBOHYDRATE FRACTIONS, TIMOTHY PROTEIN, AND DIPHTHERIA TOXIN ON THE MOTILITY OF SPERMATOZOA FROM NORMAL AND TUBERCULOUS ANIMALS

per cubic centimetre equalled that of the *TPA* solution (so adjusted because Seibert (6) had found the potency of tuberculin-protein fractions, as measured by the skin reaction in tuberculous guinea pigs, to bear a direct relation to the nitrogen content of the fraction) was almost identical with that given by the latter solution. Timothy-bacillus protein, which, though more toxic to tuberculous animals than to noninfected ones, is still a relatively nontoxic protein (8), and was chosen here because of this fact, gave a sharp decrease in motility comparable to that caused by very strong concentrations of synthetic medium tuberculin. The strongest solution of diphtheria toxin produced an acceleration of motility for about 3 hours; the other two concentrations had no effect on motility.

It seems consistent that, if *TPA* failed to produce an effect on motility, solutions of *TPU* containing an equal concentration of nitrogen should also fail, until it is recalled that *TPU* contains large quantities of carbohydrate (37.6 per cent). In the concentrations of *TPU* there was more carbohydrate per cubic centimetre than in the solution of the pure carbohydrate fraction, yet motility, which continued unaffected in the former, ceased abruptly in the latter. In this connection it is interesting to note that Seibert (8) was unable by repeated washing by ultrafiltration to remove the 37.6 per cent of carbohydrate from *TPU*, in spite of the fact that the carbohydrate by itself is able to pass through the same membrane. She has suggested that possibly this close association between carbohydrate and protein may explain why the *TPU* fraction failed to give a decrease in motility similar to that obtained with the free, pure carbohydrate fraction.

It is felt that the crudeness of the method used and the slenderness of the results here presented fail to warrant speculative discussion; hence no attempt is made to discuss the recent efforts of certain workers (9) to demonstrate the transmission of protein hypersensitiveness to offspring.

CONCLUSIONS

1. By the motility test as used in these experiments, spermatozoa from tuberculous animals could not be shown to be hypersensitive to strong concentrations of tuberculin or to purified tuberculin-protein fractions. The method therefore is not a suitable one for testing the potency of tuberculins.

2. Spermatozoa from tuberculous animals are apt to be slightly less motile and to sustain their motility less well in Locke's solution than spermatozoa from noninfected animals.

3. Strong concentrations of synthetic-medium tuberculin caused an initial acceleration of motility in spermatozoa from both normal and tuberculous animals. A like acceleration is caused by similar concentrations of Long's synthetic medium alone, however. This is presumably a nonspecific effect, due perhaps to the osmotic pressure of the solutions or to a toxicity of some of the salts present.

4. Strong concentrations of tuberculin cause a rapid decrease in the motility of spermatozoa from both normal and tuberculous animals; a similar, but less rapid, decrease is caused by equal concentrations of synthetic medium. A carbohydrate fraction derived from tuberculin and a timothy-bacillus protein likewise lessened motility rapidly.

5. Diphtheria toxin shows no effect on motility of spermatozoa from either tuberculous or nontuberculous animals, other than an acceleration when very strong concentrations are used.

The authors are indebted to Dr. Esmond R. Long for his interest and guidance in this work.

REFERENCES

(1) Long, E. R.: Amer. Rev. Tuberc., 1924, ix, 215.
(2) Moore, C. R., and Gallagher, T. F.: Am. Jour. Anat., 1930, xlv, 39.
(3) Muschat, M.: Surg., Gynec., & Obst., 1926, xlii, 778.
(4) Moore, C. R.: Jour. Exp. Zool., 1928, l, 455.
(5) Long, E. R., and Seibert, F. B.: Amer. Rev. Tuberc., 1926, xiii, 393.
(6) Seibert, F. B., and Munday, B.: Ibid., 1932, xxv, 724.
(7) Seibert, F. B.: Personal communication.
(8) Seibert, F. B., and Munday, B.: Amer. Rev. Tuberc., 1931, xxiii, 23.
(9) Otto, R.: Ztschr. f. Hyg. u. Infectionskr., 1930, cxi, 644.

THE PATHOLOGICAL ANATOMY OF PULMONARY TUBERCULOSIS IN THE AMERICAN NEGRO AND IN THE WHITE RACE[1,2]

FRANKLIN R. EVERETT

A better understanding of the characters of tuberculosis in the Negro offers the most hopeful promise of improved methods of control. It is well known that the disease in colored people, assuming forms in some respects peculiar to the race, is marked by great frequency and high mortality. The literature on the subject contains much discussion, but few observations directed to explain their susceptibility, and heredity, environment and lack of acquired immunity have been emphasized in turn.

Some believe that the greater susceptibility of the Negro to tuberculosis is due to the lack of a natural resistance acquired by the white man through many centuries of exposure to the tubercle bacillus and transmitted in the germ-plasm. Carter (1) however noted the better response to treatment on the part of the mulatto than of the black, in spite of the popular belief throughout the South that the former has little resistance against tuberculosis. Not only did he observe clinical improvement in the mulatto more frequently, but he found that under similar conditions the light mulatto responded best and the black least well, the dark mulatto occupying a middle ground. Comparison with two institutions for white people showed a poorer response to treatment in all three groups than among the white patients, with a near approach to parity between the light mulattoes and the whites. After considering environment and finding it practically identical for the blacks and mulattoes studied by him, Carter is firm in his belief that the difference in resistance must be attributed to white ancestors of the latter.

Grandy published an article on the Negro consumptive in 1908 and at

[1] From the Henry Phipps Institute and the Department of Pathology of the University of Pennsylvania, and from the Pathological Laboratory of the Philadelphia General Hospital, Philadelphia, Pennsylvania.

[2] Thesis submitted to the Faculty of Internal Medicine of the Graduate School of the University of Pennsylvania in partial fulfilment of the requirements for the degree of Doctor of Medical Science (D. Sc. (Med.)).

that time believed his high death-rate to be due to environment. After sixteen years of observation in a clinic in which white and colored patients are seen on separate days he has revised his opinion. He (2) notes great improvements in the Negro's environment in Norfolk, Virginia, and gives an interesting comparison between the weight of white and of colored children from six to twelve years of age, the white children being, he states, much more frequently 10 per cent or more underweight than the black. Yet, in spite of advances in living conditions and in the development of the Negro child, he found the absolute death-rate from tuberculosis to be higher and the relative decline lower among the Negroes in Norfolk than among the white population. The deaths per 100,000 from tuberculosis in 1907 were 135 for the white population and 433 for the black, and, in 1923, 48 for the white and 214 for the black. These observations led Grandy to attribute the Negro death-rate from tuberculosis to an hereditary lack of resistance.

Bushnell (3), on the contrary, emphasizes environment. He admits the probability that some strains among certain races may be more resistant to tuberculosis than others because the less resistant have died out, but he does not believe that an increased predisposition or an increased resistance to the disease can be inherited. He likewise opposes the suggestion that susceptibility is explicable as a lack of acquired immunity, arguing that the colored people have been in contact with white people so long that both are equally "tuberculized."

In a paper on clinically manifest and latent tuberculosis in the Negro race Opie (4) has described observations made in St. Louis, Missouri. Scars of a first infection, that is, the "childhood type" of tuberculosis in the white race, seen at autopsy are somewhat less prevalent in colored than in white adults. Apical tuberculosis, both clinically manifest and latent, the form characteristic of a reinfection, occurs less frequently in colored adults. When fatal tuberculosis occurs in the adult Negro it often has the characters of a first infection, and lesions such as acute miliary tuberculosis and lymph-node involvement, which are often seen in white children, are found much more frequently in colored than in white adults.

The acute types of tuberculosis, with which tubercle bacilli are eliminated in great number during a short time, unlike the chronic disease of white adults are not adapted to scatter tubercle bacilli in small doses over long periods. Opie emphasizes the importance of environment and the "massive infection with tubercle bacilli" to which colored people are

often exposed by the crowding of their homes and often by careless habits. The adult, he says, even though he has escaped infection during childhood, is not more susceptible than the child, and presumably does not suffer with fatal tuberculosis solely because he has come for the first time into contact with the infecting agent. A few tubercle bacilli received during childhood or adult life will doubtless produce trivial lesions, which readily heal.

What we know about the living conditions and habits of the poorer colored people indicates that contagion within the household will bring about transfer of tubercle bacilli in massive dosage from the sick to the well. Thus it seems probable that in this country, when the colored child or adult is first exposed to tuberculosis, he is more often than the white child exposed for a comparatively short time to massive "doses" of tubercle bacilli, expelled by some member of the household with acute disease, and so is more likely to receive an overwhelming infection, causing death with a lesion that resembles that of the young white child.

Methods Employed: The studies to be reported were undertaken at the Henry Phipps Institute, in the wards for tuberculosis and the Laboratory of Pathological Anatomy of the Philadelphia General Hospital and in the Pathological Laboratory of the University of Pennsylvania. The autopsies of 402 persons were studied, of which somewhat less than half were Negroes. Forty-four colored and 21 white people had died with pulmonary tuberculosis; two colored people had died of tuberculosis peritonitis; 335 persons had died from other causes and tuberculosis had not been recognized in them during life, but, among these, latent lesions were found at autopsy in 197 white and in 109 colored people. The following method was used in studying the lungs, both of those who had died with tuberculosis and those who had died of other diseases.

Roentgenograms of the chest of the living patient were taken when possible, and films were made of the chest of the cadaver before the body was opened, and of the excised inflated lungs. The lungs were hardened in formalin (10 per cent) and carefully dissected, a comparison being made between the lesions revealed by dissection and those visible in the films.

The lungs were carefully removed intact, with enough of the trachea to admit the end of a tube connected with a foot-bellows. They were inflated and placed in position for exposure. The anterior borders of the lungs were turned outward, so that the tracheal and bronchial lymph nodes were exposed, thus facilitating the location of tuberculous lesions in

these nodes. Since a subsidence of the inflated lungs was unavoidable the time of exposure was as short as possible and a much higher voltage was employed than for the cadaver.

After the fresh lungs were described uncut, as far as possible, the specimen was hardened in strong formalin. For this purpose low crocks of large diameter were used, so that the lungs floating free upon the surface of the solution would preserve their normal contour. They were turned after immersion for twenty-four hours. The lungs were then carefully and completely explored by dissection, guided by the roentgenograph placed in a viewing-box nearby. All lesions suggestive of tuberculosis were recorded and diagrams were made.

CLASSIFICATION OF LESIONS

An attempt has been made to distinguish two well known types of tuberculosis, namely, the *childhood* and the *adult.*

With the childhood type there is a tuberculous lesion in the lung substance, in a large percentage of cases situated below the pleura. There is a rapid extension of the tuberculous process to the nearest lymph nodes, where it is usually much more conspicuous than in the lung. If the process is arrested both foci become encapsulated, heal with calcification, and remain as calcified scars throughout life. On the other hand, when the disease progresses, extensive involvement of the lymph nodes with caseation may give rise to miliary tuberculosis, tuberculous meningitis or localized lesions in other parts of the body.

Lesions of the childhood type were divided into those recognizable clinically and latent lesions. They were described as follows: caseous, caseous encapsulated, caseous calcified (putty-like), calcified (mortar-like or stony hard).

Pulmonary tuberculosis of the adult type begins in one or the other apex, and tends to remain localized in the lung; the lymph nodes are not involved in the process and chronicity, as indicated by the formation of fibrous tissue, is an outstanding character. Such lesions have been separated into those that were latent and those that were manifested during life by symptoms or physical signs. The following descriptive terms have been used: *caseous tuberculosis of the apex* (tubercles with caseation but no fibrous encapsulation), *fibrocaseous tuberculosis of the apex,* and *fibrous and calcified tuberculosis of the apex.*

Fibrous apical scars, penetrating from the pleura into the substance of the lung, having no caseation or calcification and microscopically devoid

of characteristic tuberculous lesions, are not demonstrably tuberculous although they are probably with few exceptions scars of preëxisting tuberculous infection. Localized fibrous thickening of the apical pleura is perhaps due to tuberculosis in many instances, but this relation is not demonstrable.

Opie (5) (6) has shown that on the one hand the adult type of tuberculosis may occur in young children who have undergone first infection with tuberculosis and have encapsulated caseous lesions or calcified scars of tuberculosis in lungs and adjacent lymph nodes. On the other hand, the childhood type of pulmonary tuberculosis characterized by caseation of adjacent lymph nodes may occur in adults who have escaped first infection during childhood. In many instances the lesion like that of infants and young children does not begin in the apex. Nevertheless the present study has shown that a considerable number of pulmonary lesions in Negro adults have their origin in the apex, even though the adjacent lymph nodes are involved and the disease in the latter respect conforms with the childhood type. Hence these lesions are intermediate between the usual childhood and adult types of the disease.

Among 9 instances of pulmonary tuberculosis in adult Jamaican Negroes Opie (7) found 5 cases of the childhood type of tuberculosis with extraäpical lesions, but 3 lesions that had arisen in the apex had involved the adjacent lymph nodes.

The characters of the childhood and adult types of tuberculosis are contrasted in the following table:

Pulmonary Tuberculosis

Childhood Type	*Adult Type*
Lesion arises in any part of the lung	Lesion arises in the apex of the lung
The nearest lymph nodes are enlarged by tuberculous lesions and caseation occurs	There is inconspicuous if any involvement of adjacent lymph nodes
In infancy the lesion progresses rapidly, with little fibrosis, but in later childhood usually heals with encapsulation and calcification	Lesion pursues a chronic course with fibrous-tissue formation
Cavity-formation occurs with comparative infrequency	When progressive it is almost invariably accompanied by cavity-formation
Dissemination with miliary tubercles, tuberculous meningitis or other disseminated tuberculosis is common in infancy and early childhood	Dissemination seldom occurs except in the terminal stages

Table 1 shows the incidence in whites and blacks of the predominant lesions found in the autopsies studied.

TABLE 1

Incidence and classification of tuberculous lesions in autopsies

RACE	CHILDHOOD TYPE		LESIONS OF ADULT TYPE	TUBERCULOUS PERITONITIS	LATENT TUBERCULOUS LESIONS	NO TUBERCULOSIS FOUND	TOTAL
	Extra-apical lesion	With apical lesion					
White	1	1	19	0	197	12	230
Black	9	13	22	2	109	17	172

Table 1 shows that in the entire series of 402 autopsies, of which somewhat less than half were Negroes, the childhood type of pulmonary tuberculosis occurred only twice in white adults, but in half of the 44 colored people who died with tuberculosis.

The ages of those who had died from pulmonary tuberculosis (tables 2 and 3) was somewhat greater among the whites than among the Negroes, owing largely to the inclusion of 5 persons over 50 years of age among the former. These figures do not define the age incidence of the disease in the two races but are cited to show the ages of those whose lungs were examined.

TABLE 2

Distribution in age-groups of persons who died with tuberculosis

YEARS	15–20	21–25	26–30	31–35	36–40	41–45	46–50	51–55	56–60	61–65	66–70	TOTAL
Blacks	7	11	8	4	9	2	2	1	0	0	0	44
Whites	0	4	3	2	3	2	2	0	1	1	3	21

TABLE 3

Average and median age at death and duration of illness for the two races

	AVERAGE AGE	MEDIAN AGE	AVERAGE DURATION OF ILLNESS	MEDIAN DURATION OF ILLNESS
	years	*years*	*months*	*months*
Blacks	29.7	28	9.87	7
Whites	41	38	30.9	24

The average and median ages did not differ widely in the two racial groups. The shortest period of recorded illness among the colored was 1 month and the longest 4 years, the average being 9.38 months and the median 8.21.

Tuberculosis has evidently pursued a much more acute course in the black than in the white people studied.

Table 4 shows the distribution of the two sexes among the persons who died with pulmonary tuberculosis. The disease seems to have pursued a somewhat more acute course in Negro men than in Negro women, the reverse occurring among the white persons, but it is uncertain if a larger series of cases would confirm these observations. It was clearly much more acute among the colored patients of both sexes than among the white patients.

TABLE 4

Average and median age at death and duration of illness for sexes

		NUMBER	AVERAGE AGE	MEDIAN AGE	NUMBER WITH DURATION KNOWN	AVERAGE DURATION OF ILLNESS	MEDIAN DURATION
Negroes	Male	25	30.76	32	22	8.31	7
	Female	19	28.8	25	19	11.6	8
Whites	Male	12	47.9	45	7	36.4	24
	Female	9	31.8	29	8	26.1	24.5

The average and median ages of the women with tuberculosis were lower than those of the men in both races.

ADULT TYPE OF PULMONARY TUBERCULOSIS IN NEGROES

There were 22 instances (plates 1 and 2) of the adult type of pulmonary tuberculosis among Negroes, 13 in males and 9 in females, the youngest person affected being 20 years of age and the oldest 49.

The characters of the adult type of pulmonary tuberculosis in the Negro race may be compared with those in the white by discussing in turn the occurrence of tuberculous pneumonia, excavation and fibrous-tissue formation.

The extent to which one or both lungs were involved by caseous pneumonia varied widely. In some instances there was more or less widespread tuberculous bronchopneumonia; in others secondary lobules or groups of lobules were the site of tuberculous pneumonia. Caseous pneumonia has been designated "massive" only when a whole lobe or its equivalent was consolidated by tuberculous pneumonia. Among the 22 cases of adult-type pulmonary tuberculosis in Negroes there were 9 with massive tuberculous pneumonia.

Fibrous tissue, abundant in all tuberculous lesions that pursue a chronic course, is presumably formed when some part of the lesion is in process

of healing and may be regarded roughly as an index of resistance to the disease. Fibrous-tissue formation was considered slight or absent in 5 instances, moderate in 13 and advanced in 4. This estimate is based upon the gross appearance of the lesion and will serve as a rough basis of comparison with similar changes in the white race.

There were cavities in all the cases of pulmonary tuberculosis of adult type. Particular attention was paid to the character of their walls. In 14 cases these were sharply defined, and the lining, being smooth, was evidently in process of organization. In 5 instances there were no organized walls, these ulcerative cavities being formed within areas of caseous consolidation and lined by ragged caseous material. In 3 instances the walls of some cavities were smooth and the walls of others ragged and necrotic. The characters of the cavity are doubtless in large part determined by the factors that control fibrous-tissue formation.

Healing or healed lesions of a first infection with tuberculosis are represented by caseous or calcified lesions encapsulated by fibrous tissue in the lung substance, accompanied by caseous encapsulated or calcified lesions in adjacent lymph nodes (the "primary complex" of German writers). When they occur in lungs with progressive tuberculosis of adult type it may be assumed that they are lesions of first infection preceding the apical lesion of later life. Among the 22 instances of the adult type of pulmonary tuberculosis in Negroes evidence of a first infection was found in the lung in 15.

In two instances (nos. 17 and 18) the roentgenographs showed what appeared to be the shadows of calcified nodules in the lung, but in neither could corresponding lesions be found by dissection. Both of these cases were evidently of adult type and the occurrence of extensive consolidation of lung tissue in both may have increased the difficulty of finding small calcified nodules.

In 4 instances of the adult type of pulmonary tuberculosis (nos. 1, 2, 7 and 14) no primary lesion could be found either by dissection or with the aid of roentgenographs. It is not improbable that small nodules embedded in dense tuberculous tissue escape detection either by X-ray examination of the excised lung or by dissection.

In one case, no. 1, the first infection doubtless occurred by way of the gastrointestinal tract, for the mesentery contained a calcified lymph node of mortar-like consistency and other nodes that were caseous. In this instance it is possible that the calcified nodule represents an old lesion, perhaps acquired in childhood, whereas the caseous lesions are the

result of a more recent infection, being perhaps part of the terminal generalized tuberculosis with laryngitis, enteritis and peritonitis, that occurred in this patient in association with far-advanced bilateral pulmonary disease.

CHILDHOOD TYPE OF PULMONARY TUBERCULOSIS IN ADULT NEGROES

The occurrence of caseous tuberculosis in lymph nodes in the line of lymphatic drainage from a tuberculous focus in the lung has been accepted as evidence of first infection; 22 lesions with lymph-node involvement found in the 44 cases of pulmonary tuberculosis in adult Negroes have been designated as the childhood type of the disease. They fall into two groups: (1) those with the pulmonary lesion not situated in the apex and (2) those with the pulmonary lesion more advanced in the apex than elsewhere, in this respect resembling the adult type but regarded as of childhood type because the lymph nodes were caseous.

1: Childhood Type with Pulmonary Lesion Not in Apex of Lung

There were 9 instances (plate 3) of the childhood type of pulmonary tuberculosis that did not arise in the apex. Of this group 5 were men and 4 women. The youngest was 17 years old and the eldest 44, the average and median ages being 25 and 23 years respectively. The shortest period of recorded illness was 3 months and the longest 24 months, with 8 and 7 months respectively as the average and median.

In the 9 cases under consideration the caseous tracheobronchial lymph nodes and the pulmonary areas of caseation ranged from small foci, 2 to 3 mm. across, to a mass almost homogeneously caseous, measuring 10 by 5 cm., and the number of nodes affected in any one case varied from one to twenty-one. The wide divergence in the extent of involvement of the tracheobronchial lymph nodes is especially noteworthy, varying from two small areas (no. 23) to numerous immensely enlarged lymph nodes almost entirely replaced by caseous material (for instance, no. 26).

Tuberculous pneumonia was entirely absent in one instance (no. 27), and massive in four.

Fibrous tissue was lacking in 6 instances, scant in two and advanced in one. Two cases (nos. 28 and 30) will be described as chronic progressive tuberculosis of childhood type.

Cavities were found in 5 of the 9 cases, in 3 with caseous walls and in 2 with smooth walls. In no. 30 there was no excavation and in no. 28 there were cavities with smooth walls.

There was evidence of a first infection preceding that which was progressive at the time of death in only one of the 9 cases included in this group. In this instance (no. 30) chronic fibroid tuberculosis, most advanced in the right lower lobe and accompanied by disseminated hyaline tubercles, occurred in a man 32 years of age; firmly calcified nodules, evidently the result of an earlier infection, were found in lungs and lymph nodes. Animal experiments show that both hypersensitiveness to tuberculin and resistance to reinfection disappear with complete recovery from a first infection, and in persons who have recovered from tuberculous infection the tuberculin reaction may become negative. Hence it is not improbable that in this instance reinfection occurred at a time when recovery from the first infection was so complete that the second infection assumed the type of a first infection. It is possible that its chronic course and the fibroid character of the lesion are manifestations of some remaining resistance.

In case no. 24, lymph nodes contained both encapsulated and progressive foci of caseation, but since one caseous focus had broken through the lymph node into the lung parenchyma it is evident that the disease was healing in one place and spreading in another. In case no. 26, there were caseous tracheobronchial and mesenteric lymph nodes, in some of which, in both groups, calcium had been deposited in soft caseous material in sufficient quantity to cast a shadow upon an X-ray film prepared from the excised tissue.

In the 9 cases enumerated acute miliary tuberculosis occurred twice. Tuberculous enteritis was found 6 times, caseous tuberculosis of mesenteric lymph nodes twice and tuberculous peritonitis 3 times.

Localized Pleural Tuberculosis with Pulmonary Tuberculosis of Childhood Type: An unusual case (no. 27) of this childhood-type group deserves special discussion. In a colored man, aged 22 years, whose health had been poor for 7 months, there was massive caseous tuberculosis of the pleura of the right lung, beginning close to the tip of the apex and extending the entire length of the upper lobe and over the upper half of the middle lobe. The pulmonary tissue beneath the caseous pleura was involved, and the lymph nodes of the right hilum and the tracheobronchial lymph nodes on the right of the trachea were grossly caseous. An X-ray plate made from the excised lungs and dissection of the lung revealed no evidence of a preceding infection. The lack of such evidence strengthens the view that this lesion is primary and had its origin in the lung tissue just beneath the pleura of the right upper lobe with extension over the pleural surface and involvement of bronchial and tracheobronchial lymph nodes.

This case evidently belongs to a group of pleural lesions characterized by localized spread from the lung to the overlying pleura. Opie (4) describes a case that closely resembles the foregoing. A colored woman, aged 26 years, was admitted to the Barnes Hospital of St. Louis in the seventh month of gestation with a "cold in the chest," which had persisted for 6 weeks. At the lowermost anterior part of the right lower lobe, projecting upon the pleural surface of the lung but penetrating into the parenchyma, there was a firm mass, in part gray and in part opaque, yellow and caseous; it was spread over the pleura and measured 6 cm. across and 2.5 cm. in thickness; it was smooth on its pleural aspect and nodular where in contact with the lung substance. In the midpart of the lower lobe there was a caseous lymph node, and below the right bronchus and the bifurcation of the trachea, and above the right bronchus beside the trachea, there were immense caseous lymph-node masses. The lungs and other organs were thickly studded with miliary tubercles. An X-ray plate made from the excised lungs and careful dissection gave no evidence of any older calcified or encapsulated lesion in lungs or tracheobronchial lymph nodes.

Hetherington, McPhedran, Landis and Opie (8) describe two lesions of a similar nature, recognized in roentgenographs of the chests of school children. One was observed in a colored boy, aged 7 years, who reacted intensely to tuberculin. Roentgenological examination showed a large, clearly outlined, oval mass over the pleura in the left axilla; the lesion was unaccompanied by physical signs or significant symptoms. The second occurred in a boy of Lithuanian parentage, aged 19 years, whose father was apparently ill with pulmonary tuberculosis. The boy reacted intensely to tuberculin, and roentgenological examination disclosed a fairly homogeneous opacity, from 2 to 4 cm. in thickness, extending over the diaphragm from the heart-border to the lateral chest-wall on the left. An oblique film showed that this lesion was close to the posterior chest-wall and involved the pleura with strands extending into the lung substance. There were restricted movement of the left diaphragm and feeble breath-sounds at the base of the left lung.

All of these lesions had the characteristics of the childhood type of pulmonary tuberculosis. There was infiltration of the lung parenchyma beneath the pleura, with extension to and involvement of the pleura, and, as seen at autopsy in the one instance, simultaneous spread to the lymph nodes at the hilum, and about the bronchi and trachea.

Chronic Progressive Tuberculosis of Childhood Type: Usually when

tuberculosis of childhood type causes death during adult life the disease pursues a rapid course and is associated with massive caseous pneumonia, with ulcerative cavities and scant, if any, fibrous tissue. Among the instances of childhood-type tuberculosis in adult Negroes 2 cases were of outstanding interest because the lesions were chronic and progressive.

A black woman (no. 28), aged 23 years, had been ill for a little more than two years. The whole right lower lobe, which was consolidated throughout and in large part caseous, contained cavities with fairly smooth but partly caseous walls; two lymph nodes at the hilum of the right lung contained caseous spots. There was caseous consolidation with cavity-formation in the lower part of the left upper lobe. Microscopic examination of the lung showed fibrous tissue in moderate amount about tubercles, and granulation tissue with fibrous tissue in the walls of cavities. Tubercle bacilli of human type were obtained by animal inoculation and cultivation from the pneumonic lung substance.

In this instance death followed a prolonged illness. Tuberculosis evidently had its origin in the right lower lobe and there was scant caseation of adjacent lymph nodes, but the lesion otherwise had the characters of chronic pulmonary tuberculosis.

In the second instance, a man (no. 30) died at the age of 32 after an illness of uncertain duration. The lungs contained several small, firmly calcified nodules and there was a small firmly calcified nodule in a lymph node in contact with the right bronchus. The right lower lobe was the site of tuberculous consolidation, which had been in considerable part transformed into fibrous tissue. Throughout the lungs there were healed tubercles collected into groups that suggested a bronchial origin. At the hilum of the right lung and at the bifurcation of the trachea there were immense lymph-node masses containing hyaline tubercles and caseous spots surrounded by fibrous tissue. In the lungs and lymph nodes there was a fresh crop of small caseous tubercles largely composed of epithelioid cells.

No exact interpretation of the pathogenesis of the lesions in this instance can be given. As suggested on page 420, it is possible that immunity conferred by a first infection, represented by old calcified lesions in lungs and lymph nodes, had almost wholly disappeared so that on reinfection the childhood type was again possible. Some scant remaining immunity had perhaps induced a chronic course, with fibrous and hyaline degeneration of tubercles, but was insufficient to bring about complete healing with total destruction of tubercle bacilli. It is however possible that the early infection represented at autopsy by calcified foci in lungs and lymph

nodes, though healed in part, had progressed elsewhere, finally causing death.

2: Childhood Type with Primary Localization in the Apex

In the entire series of autopsies there were 13 instances (plate 4) of pulmonary tuberculosis, all in Negroes, that did not strictly conform to either of the recognized types of tuberculosis, because, although the disease resembled the childhood type in that there were caseous foci in the lungs and lymph nodes, it had its origin in the apex of the lung, like the adult type. Apical localization accompanied by caseous tuberculosis of adjacent lymph nodes evidently occurs much more frequently in adults than in children. Physiological changes occurring with the transition from childhood to adult life probably determine the relative susceptibility of the apex to tuberculosis. Involvement of lymph nodes, on the contrary, in man as in experimental animals, is referable to natural susceptibility, which is lost when immunization follows first infection.

Of the 13 cases in this group 7 were in men and 6 in women, with an age range from 17 to 54 years, the average and median ages being 32.2 and 28.12 years respectively. These are considerably higher than the corresponding figures for the lesions that did not arise in the apex (average 25 years, median 23 years). The duration of illness was from 2 to 24 months, with an average and median duration of 9.5 and 9.37 months respectively. These figures are again larger than those for extraäpical lesions of childhood type (average 8 months, median 7 months).

In more than half of these instances of the childhood type of pulmonary tuberculosis with apical involvement there was massive tuberculous pneumonia (8 of 13, or 61.5 per cent). There were cavities with ragged caseous walls in 5 cases and the walls were smooth with evident organization in the remaining eight. There was no instance of advanced fibrous-tissue formation, such as was seen in a few cases of the adult type of pulmonary tuberculosis in Negroes, but moderate fibrosis occurred five times and slight fibrosis four times.

Evidence of a first infection preceding the fatal lesion was sought and in all except one case (no. 44) X-ray and dissection failed to reveal calcified or encapsulated scars of an infection presumably older than that which caused death.

Calcification does not necessarily indicate a lesion of earlier infection, for a lesion that is progressing in one part may be undergoing calcification elsewhere.

In a young woman (no. 32) there was massive tuberculous pneumonia, most advanced in the apices, and caseous tracheobronchial lymph nodes. In the mesentery there were lymph nodes containing caseous encapsulated spots, within which X-ray films showed the presence of calcium. Doubtless infection had begun simultaneously in lungs and intestine; it had progressed in the former, though the lesions of the mesenteric lymph nodes were undergoing encapsulation and beginning calcification.

In another young woman (no. 33), aged 18 years, who was said to have been sick for two or three years, there was apical pulmonary tuberculosis and caseation with beginning calcification of tracheobronchial lymph nodes. Moderately enlarged lymph nodes within the substance of the right lung contained conspicuous caseous foci. In lymph nodes below the bronchi there was caseation with no gross evidence of calcification, but in two spots caseous material of putty-like consistence was shown to be conspicuously calcified in X-ray films of the excised lungs, though it did not grit when cut. In the ileum there were tuberculous ulcers, and in two mesenteric lymph nodes firm caseous spots, which contained enough calcium to make them very conspicuous in X-ray plates though calcium was not grossly apparent. The disease probably had its origin simultaneously in lung and intestine and evidently pursued a chronic course. In both the tracheobronchial and mesenteric lymph nodes there was progressive caseous tuberculosis associated with foci of beginning calcification well defined in roentgenographs. In this case calcification and progressive tuberculosis were simultaneous, and both presumably the result of the same infectious process.

In one instance old stony-hard calcified lesions in the lymph nodes were, on the contrary, the healed remains of tuberculous infection that preceded the fatal disease. A colored woman (no. 44), aged 54 years, had been ill seven months before death. There was tuberculous consolidation of the upper part of both upper lobes, with smooth thin-walled cavities at each apex. There were three partly caseous lymph nodes within the lung at the right hilum. Beneath the right bronchus there was a lymph node containing numerous small scattered stony-hard nodules and one encapsulated mass consisting of small separable particles of hard calcified material. In this elderly woman, in association with tuberculosis of childhood type though of apical origin, was the firmly calcified scar of a preceding infection. The evidence to support the opinion that resistance consequent upon a first infection may so completely disappear that rein-

fection assumes the characters of the childhood type of tuberculosis has already been discussed.

EXTRAPULMONARY TUBERCULOSIS IN NEGRO ADULTS

In two cases tuberculous peritonitis in Negro adults was the cause of death. (See table 1.) In one instance in a woman aged 23 years the peritoneal surface was studded with tubercles and bound together by adhesions; in the ileum were tuberculous ulcers. There were flat nodules upon the right visceral pleura and caseous foci in a lymph node at the left hilum. In the other case, in a woman aged 25 years, the intestines were densely matted together by adhesions and caseous tubercles. The mesenteric lymph nodes were caseous. No tuberculosis of the lungs was found, but there were caseous lesions in four tracheobronchial lymph nodes.

Tuberculous peritonitis was present in 5 of the 22 Negro adults with the childhood type of pulmonary tuberculosis (nos. 24, 25, 27, 32 and 35), and once in the 22 instances of the adult type in Negroes, but it did not occur in any of the 21 instances of fatal pulmonary tuberculosis in white adults.

Acute miliary tuberculosis occurred only twice in the entire series and in both instances was associated with the childhood type of extraäpical pulmonary tuberculosis in adult Negroes (nos. 26 and 31). The association of miliary tuberculosis with the childhood type of pulmonary tuberculosis in white and colored adults has been discussed by Opie (4) (5).

Tuberculous meningitis occurred twice, in both instances associated with the adult type of pulmonary tuberculosis in white adults.

PULMONARY TUBERCULOSIS OF ADULT TYPE IN WHITE ADULTS

The adult type of pulmonary tuberculosis was found in 19 of the 21 white people who had died with pulmonary tuberculosis (plates 5 and 6). The youngest of this group was 21 years of age and the oldest 70, giving 36 years as the average and 36.2 years as the median ages. The shortest period of recorded illness was 1 month and the longest 10 years, the average duration being 33.3 months and the median 27.5 months. The average and median ages for the male were 40.5 and 36.6 months respectively; for the female the average was 31.5 and the median 28.75 months.

In 15 cases of adult-type tuberculosis in white people healed or healing lesions of a first infection were found by dissection of the lungs

and tracheobronchial lymph nodes, and in the 4 remaining cases calcified lesions were indicated by shadows in roentgenographs but were not discovered in the lung by dissection. It is noteworthy that the foci demonstrated by dissection totalled 49 lesions in lungs and lymph nodes, of which 43 were firmly calcified, 4 caseous-calcified, and only 2 caseous-encapsulated. In two instances (nos. 47 and 58) there were calcified nodes in the mesentery; it is significant that in these cases there were calcified nodules of the lungs and lymph nodes as well, infection by way of the respiratory and alimentary tracts having perhaps been simultaneous.

Advanced fibrosis occurred in all but 4 instances, nos. 45, 46, 47 and 63, and in these it was present to a moderate extent.

Cavities occurred in all cases and in all but one they had smooth organized walls. In this case, no. 45, the walls of some cavities were fairly well defined, but a larger number had a ragged necrotic lining. With this lesion there was only moderate fibrosis.

Tuberculous pneumonia when present was of slight extent and was absent in 8 instances.

CHILDHOOD TYPE OF PULMONARY TUBERCULOSIS IN WHITE ADULTS

Among the 21 adult white persons who died with pulmonary tuberculosis there were only two with the childhood type of the disease, one having its origin at the apex and the other near the base of the lungs.

In a man aged 50 years with endocarditis and cirrhosis of the liver there was chronic pulmonary tuberculosis of both apices with some tuberculous pneumonia above the right bronchus, and at the bifurcation of the trachea there were enlarged caseous lymph nodes. Death occurred with tuberculous meningitis.

A white woman aged 27 years had had what was believed to be pneumonia followed by empyema two years before her death. Tuberculosis was limited to the right lower lobe and the adjacent lymph nodes. No evidence of a preëxisting tuberculous lesion could be detected by X-ray examination of the excised lung or by dissection and, moreover, the fatal lesion was typical of a first infection. The process evidently had its origin in the right lower lobe beneath the pleura and, as the lesion progressed and caseation developed, a communication was established between the lung substance and the pleural cavity. There was extensive caseation of pulmonary lymph nodes.

COMPARISON OF LESIONS IN THE AMERICAN NEGRO AND IN WHITE PERSONS

Table 5 assembles data that show conspicuous differences between the tuberculosis of the American Negro and that of white people living in the same city.

TABLE 5

Comparison of lesions in American Negro and in white persons (adults)

	NUMBER OF CASES	AVERAGE DURATION OF DISEASE IN MONTHS	CASES WITH TUBERCULOUS PNEUMONIA	CASES WITH CAVITIES HAVING NECROTIC WALL	CASES WITH CAVITIES HAVING SMOOTH WALL	CASES WITH MODERATE FIBROSIS	CASES WITH ADVANCED FIBROSIS	CASES WITH LESIONS OF PRECEDING INFECTION
Negro:								
Adult type.....	22	9.1	9	8	14	13	4	15
Childhood type.....	22	9.8	12	8	9	5	1	2
White:								
Adult type.....	19	30	0	1	18	5	14	15
Childhood type.....	2		0	1	1	1	1	0

Since the number of cases of the adult and childhood types of tuberculosis in adult Negroes is the same, the figures representing the various lesions listed are comparable. On the one hand, massive tuberculous pneumonia is seen to be more common with the childhood type of the disease, whereas on the other hand processes associated with fibrosis, such as organization of the walls of cavities and the formation of fibroid tissue, are more frequent with the adult type. In 15 of 22 instances of the latter, lesions of first infection were found by dissection and in two more cases they were suggested by X-ray shadows; consolidation of the lung by tuberculous lesions may conceal the scars of first infection and formation of cavities may bring about their obliteration. In two instances of the childhood type of tuberculosis there were stony-hard calcified scars of first infection, and it is not improbable that in these cases resistance to reinfection had been largely lost.

Comparison between the lesions of white and Negro adults is even more instructive. The disease pursues a much more rapid course in Negroes. Acute pneumonic lesions are much more frequent and advanced in the colored man, but fibrous-tissue formation, as indicated by smooth-walled cavities and fibrosis, is far more conspicuous in the white man than in the Negro. With the adult type of tuberculosis in white persons lesions of

first infection were found 15 times and in the other 4 cases were suggested in roentgenographs.

LATENT TUBERCULOSIS

Among the 335 autopsies of persons who had died from diseases other than tuberculosis 306 were found to have tuberculous lesions that were regarded as latent because signs and symptoms of the disease had not been recognized during life. The number of white people represented by these autopsies, that is, 197, was somewhat greater than the number of colored people, one hundred and nine. The latent focal lesions of childhood type found in lungs and lymph nodes and the latent apical lesions will be considered separately and their incidence in white and colored people will be compared.

Latent Tuberculous Foci of Lungs and Lymph Nodes: In most of the cases all of the latent childhood-type lesions found in any one pair of lungs were of the same character, being (a) caseous, (b) caseous and encapsulated, (c) caseous and calcified, or (d) calcified, but not infrequently a multiplicity of these kinds occurred.

Table 6 shows the incidence of latent lesions of childhood type in the stages enumerated, and combinations of lesions in two or more stages in the same person.

TABLE 6

Latent tuberculous lesions of childhood type in lungs and lymph nodes of persons who died of other diseases

STAGE OF LESIONS	WHITE		BLACK	
	Male	Female	Male	Female
Caseous	2			
Caseous + caseous-encapsulated		5		1
Caseous + caseous-encapsulated + calcified	3		1	1
Caseous + calcified	1	1	3	2
Caseous + caseous-calcified + calcified	1	1		
Caseous-encapsulated	3	2	2	
Caseous-encapsulated + caseous-calcified	1	1		
Caseous-encapsulated + caseous-calcified + calcified	2	2		1
Caseous-encapsulated + calcified	12	5	5	5
Caseous-calcified	4	1	2	
Caseous-calcified + calcified	7	3	2	
Calcified	84	48	40	40
No lesion of childhood type	14	6	12	9
Total	134	75	67	59

Calcified lesions only were found in the greater number of these autopsies but numerous combinations of less completely healed lesions were also seen. The relative duration of infection cannot be accurately determined by the character of the lesion, but it is not improbable that in many instances caseous or caseous encapsulated lesions in association with calcified nodules are of more recent origin. It has been pointed out that with complete healing of tuberculous lesions sensitization and immunity against the disease may disappear; the tuberculin reaction may occasionally be negative when there is a calcified tuberculous lesion of lungs or tracheobronchial lymph nodes shown by roentgenographs of the chest.

The incidence of latent focal lesions of childhood type in Negroes (90 per cent) does not differ materially from that in white people (90.4 per cent). In St. Louis, Opie (4) found by roentgenographic examination of the excised lungs a somewhat smaller percentage of latent childhood type lesions in black than in white adults.

Latent Apical Tuberculosis: The latent lesions found at the apices of the lungs fall into the following groups: (a) caseous tuberculous lesions, (b) calcified tuberculous lesions, (c) fibrous scars of the apex and (d) fibrous thickening of the apical pleura.

Latent caseous tuberculous lesions of the apex varied from small areas in contact with the apical pleura a short distance from the summit to lesions that may occupy a third or more of the apex. Their tuberculous nature is macroscopically indicated by spots of caseation. Many of these lesions have evidently persisted for a considerable period of time, for in most instances caseous areas are surrounded and separated from each other by abundant fibrous tissue. Not infrequently, however, the lesion is evidently progressive and fresh tubercles are recognizable.

An apical lesion in which calcification has occurred may be regarded as tuberculous because caseous material undergoes calcification when healing occurs.

Fibrous apical scars doubtless represent tuberculous lesions that have undergone complete healing without calcification, since they are usually limited to the apex and often there is a caseous lesion at one apex and a fibrous scar at the other.

It is uncertain whether fibrous thickening of the apical pleura is always referable to tuberculosis but its association with tuberculous lesions in many instances indicates that it may have been caused by tuberculous infection. Table 7 shows the frequency with which the lesions of the apex that have been defined occurred in white and black persons.

TABLE 7

Latent apical tuberculous lesions of the lungs of persons who died of other diseases

STATE OF LESIONS	WHITE		BLACK		WHITE		BLACK	
	Male	Female	Male	Female	Number	Per cent	Number	Per cent
Caseous lesions	24	5	7	7	29	13.9	14	11.1
Calcified lesions	14	7	1	3	21	10	4	3.2
Fibrous scar	36	17	13	7	53	25.4	20	15.9
Fibrous thickening of the apical pleura	21	18	9	5	39	18.7	14	11.1
Focal lesion of childhood type but no apical lesion	32	23	28	29	67	32.1	74	58.7
No lesion of tuberculosis found	7	5	9	8				
Total	134	75	67	59				

It is noteworthy that no lesions of childhood type were found in association with latent apical lesions in 7 white men, in 1 white woman, in 3 Negro men and in 1 Negro woman. (Compare tables 6 and 7.)

The incidence of each of the various latent apical lesions described is expressed by a lower percentage of the Negroes than of the whites, and latent tuberculosis with no apical involvement was found in almost twice the percentage of colored people, 52.2 per cent, as of white people, 27.9 per cent. This relation is in conspicuous contrast with the mortality from the two races in Philadelphia, where these observations were made, which in 1930 was 253.3 per 100,000 for the colored race and 59 for the white race. The relative infrequency of latent apical lesions in colored people is in agreement with observations made by Opie (4) in St. Louis.

CONCLUSIONS

1. The anatomical characters of tuberculosis in the American Negro differ widely from those of the white people of the same community.

2. Tuberculosis pursues a more rapidly fatal course in the Negro than in white people; widespread tuberculous pneumonia with rapid excavation of the lung is more frequent and formation of fibrous tissue is less conspicuous in the black than in the white.

3. The adult type of pulmonary tuberculosis, which is prevalent in white adults, occurs in only half of the instances of pulmonary tuberculosis in Negroes but pursues in them a more rapid course.

4. The childhood type of pulmonary tuberculosis with caseous tuberculosis of tracheobronchial lymph nodes occurs in nearly half of Negro

adults but in only a small percentage of white adults who have died from pulmonary tuberculosis.

5. In more than half of the Negro adults with the childhood type of pulmonary tuberculosis the lesion has its origin in the apex of the lung.

6. Latent apical tuberculosis occurs considerably less frequently in Negro than in white adults.

Acknowledgment is made to Miss Eleanor S. Cooper of the Henry Phipps Institute for editorial assistance in the preparation of this paper.

REFERENCES

(1) CARTER, H. G.: Amer. Rev. Tuberc., 1926, xiv, 653.
(2) GRANDY, C. R.: Ibid., 1924, x, 275.
(3) BUSHNELL, G. E.: Epidemiology of tuberculosis, New York, 1920.
(4) OPIE, E. L.: Amer. Rev. Tuberc., 1924, x, 265.
(5) OPIE, E. L.: Jour. Exp. Med., 1917, xxvi, 263.
(6) OPIE, E. L.: Brit. M. J., Dec. 17, 1927.
(7) OPIE, E. L.: Amer. Rev. Tuberc., 1930, xxii, 613.
(8) OPIE, E. L., LANDIS, H. R. M., MCPHEDRAN, F. M. AND HETHERINGTON, H. W.: Ibid., 1929, xx, 413, 421.

PLATE 1

Adult Type of Pulmonary Tuberculosis in Negro Adults

1: Male, colored, aged 20 years. Symptoms had an acute onset 2 months before death, with pain in the chest on the right side, chilly feeling and slight cough.

Autopsy: There was a cavity, 2.5 cm. across, with a ragged but well-defined wall, surrounded by caseous consolidation of almost the entire right upper lobe; about one-half of the lower lobe was similarly consolidated. There were conglomerate tubercles in the middle lobe and scattered groups of conglomerate tubercles and a few patches of pneumonia throughout the left lung.

Diagnosis: Chronic pulmonary tuberculosis, most advanced in the right lung, with excavation, massive tuberculous pneumonia and conglomerate tubercles.

2: Female, colored, aged 21 years. Symptoms began 3 months before death with a dry cough, pain in the chest, night-sweats and loss of weight. The cough became productive and the sputum was found to contain tubercle bacilli.

Autopsy: The pleura of the entire right lung was much thickened; almost all of the upper lobe was occupied by a large cavity with a well-organized wall, surrounded by a moderate amount of fibrous tissue; the middle and lower lobes were entirely consolidated by tuberculous pneumonia. Throughout both lobes

of the left lung there were groups of conglomerate tubercles. There were tuberculous ulcers in the ileum.

Diagnosis: Chronic pulmonary tuberculosis, with extensive pleurisy, excavation, moderate fibrosis and massive tuberculous pneumonia of one lung and conglomerate tubercles in the other; tuberculous enteritis.

3: Female, colored, aged 23 years. Illness began 4 years before death with cough and expectoration. The sputum contained tubercle bacilli.

Autopsy: The pleura of the entire left lung was much thickened and the pleural cavity obliterated; section revealed cavities throughout the lung, the largest being at the apex and measuring 8 cm. across. There was tuberculous pneumonia involving a large part of the left lung, but some air-containing tissue remained in the lower part of the lower lobe. In the lower part of the right upper lobe near the hilum there were numerous small irregular communicating cavities surrounded by caseous consolidation; the lower part of the middle lobe and the anterior part of the lower lobe contained lesions with the characters of fibroid bronchopneumonia. A lymph node in the right hilum showed two calcified nodules, the larger about 0.5 cm. across. There was tuberculous appendicitis, and tuberculous ulcers in the ileum.

Diagnosis: Chronic pulmonary tuberculosis, with extensive pleurisy of the left lung, and extensive excavation, moderate fibrosis and fairly extensive tuberculous pneumonia; tuberculous appendicitis and enteritis. There were calcified foci of a first infection in tracheobronchial lymph nodes.

4: Female, colored, aged 24 years. Illness began five months before death with cough, weakness and haemoptysis. The sputum contained tubercle bacilli.

Autopsy: In the left lung all of the upper lobe except the lowermost tip, and practically all of the lower lobe were consolidated by tuberculous pneumonia; about 10 cm. from the apex of the upper lobe there was a cavity, measuring 8 x 5 cm., with caseous wall, but surrounded by a slight amount of fibrous tissue. Throughout the right lung there were conspicuous patches of tuberculous bronchopneumonia. On the surface of the right upper lobe near its lower border there was a puckered area, 2 cm. across, and below it a well-encapsulated caseous nodule; nearby was another smaller encapsulated caseous nodule.

Diagnosis: Pulmonary tuberculosis, with massive tuberculous pneumonia and excavation in left lung; tuberculous bronchopneumonia of right lung. There were caseous encapsulated foci of a first infection in lung substance.

5: Male, colored, aged 24 years. Symptoms began one year before death with loss of appetite, and six months after onset cough developed.

Autopsy: Both lungs were extensively consolidated, and in part caseous; both upper lobes contained several large and small cavities with smooth walls

ADULT TYPE OF PULMONARY TUBERCULOSIS IN NEGRO ADULTS.

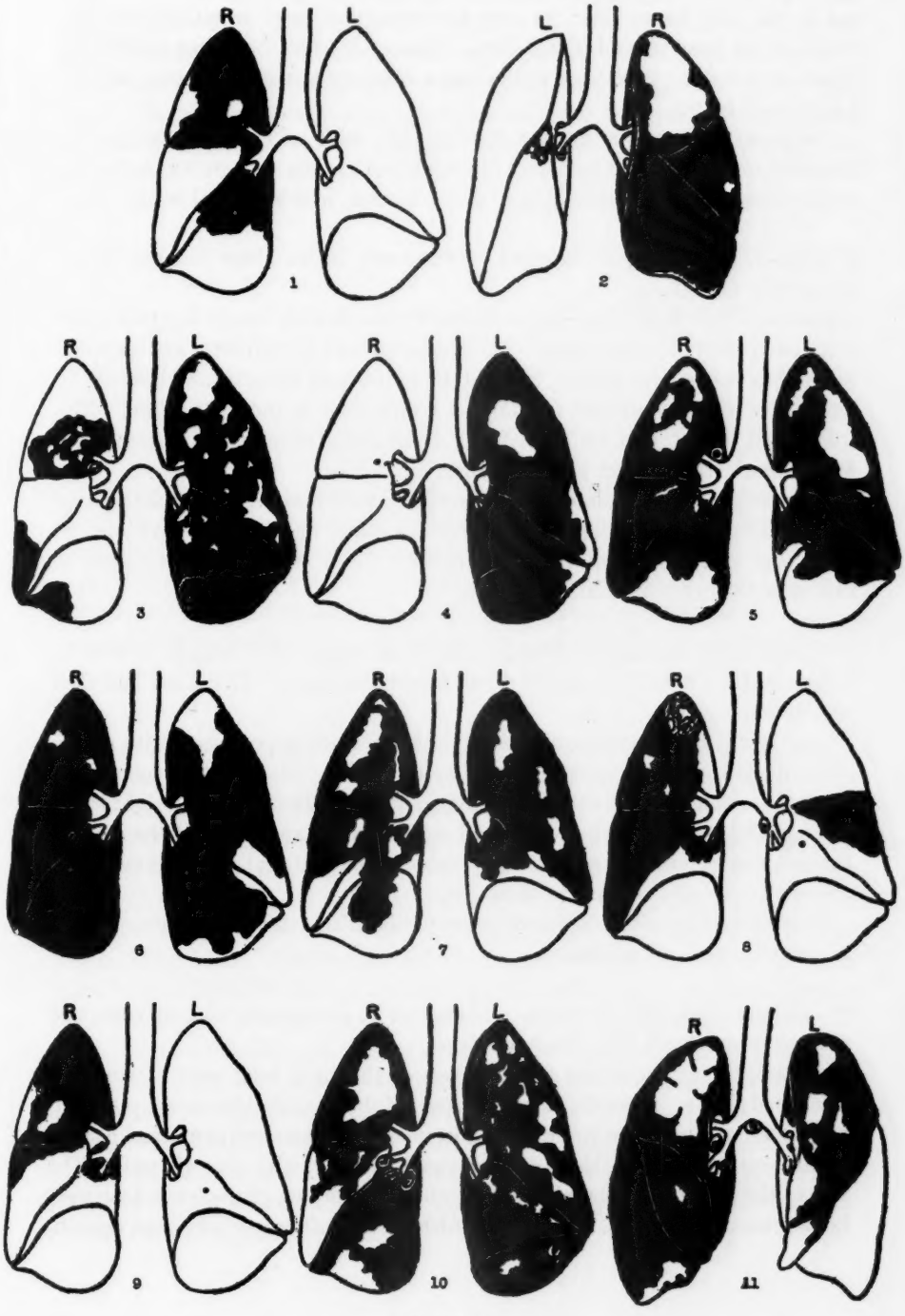


PLATE 1

and considerable fibrous tissue; there was a small cavity in the right middle and one in the right lower lobe; the only air-containing tissue in either lung was found at the base of each lower lobe. Above the right bronchus within the hilum there was a lymph node containing a small encapsulated caseous nodule, 2 mm. in diameter.

Diagnosis: Chronic pulmonary tuberculosis, with tuberculous pneumonia, extensive excavation and moderate fibrosis in both lungs. There was a caseous encapsulated nodule, presumably of first infection, in a bronchial lymph node.

6: Female, colored, aged 25 years. Symptoms began three months before death with a cough.

Autopsy: The right lung was completely consolidated except for two fairly small cavities in the upper lobe. The greater part of the left lung was occupied by caseous pneumonia, leaving air-containing tissue at the apex and base of the lung. There was a calcified nodule in a lymph node in the right hilum. The spleen and liver contained tubercles and the ileum tuberculous ulcers; there were caseous lymph nodes in the mesentery.

Diagnosis: Chronic pulmonary tuberculosis, with massive tuberculous pneumonia and slight excavation; tubercles of the spleen and liver; tuberculous enteritis and caseous mesenteric lymph nodes. There was a calcified nodule of first infection in a bronchial lymph node.

7: Female, colored, aged 25 years. Symptoms began with fatigue 13 months before death; a cough developed 4 months before death. Her sister had died with tuberculosis.

Autopsy: There was massive consolidation of both upper lobes, with extensive cavity-formation, most advanced in the right. All the other lobes were partly consolidated, and there were cavities in the right middle and right lower lobes. The larger apical cavities had smooth walls and some of the smaller cavities ragged necrotic walls. The consolidated material included considerable fibrous tissue and areas of caseation.

Diagnosis: Chronic pulmonary tuberculosis, with extensive excavation and advanced fibrosis of both lungs.

8: Male, colored, aged 26 years. There was an acute onset of symptoms two months before death with cough and fever.

Autopsy: The upper and middle lobes of the right lung were covered by thickened pleura. Over the external aspect of the apex the pleura was puckered and adherent, and below it the lung substance was fibrous and contained a small smooth-walled cavity. Nearby was a smaller cavity, with necrotic wall. The rest of the upper lobe, the middle lobe and a small part of the lower lobe were homogeneously caseous. About one-fifth of the left upper lobe was consoli-

dated. In the left lower lobe, 0.5 cm. beneath the posterior surface, near the hilum there was a firmly calcified nodule, 4 mm. in diameter, and another stony-hard nodule, 2 mm. across, in a lymph node beneath the left bronchus.

Diagnosis: Chronic pulmonary tuberculosis, most advanced in the right lung, with chronic pleurisy, excavation, localized fibrosis and massive tuberculous pneumonia. There were calcified foci of a first infection in lung and lymph node.

9: Male, colored, aged 28 years. Illness began more than 2 years before death with cough, night-sweats and loss of weight.

Autopsy: Near the right apex there were caseous foci surrounded by fibrous tissue. The greater part of the right upper lobe was consolidated by patches of tuberculous pneumonia, and within this area in the lower part of the lobe there was a smooth-walled cavity, 5 cm. across, surrounded by a moderate amount of fibrous tissue; elsewhere in the lung were conglomerate tubercles, in places thickly studded. Upon the external aspect of the lower left lobe, within the pleura, there was a spherical caseous-calcified nodule, 2.5 mm. across, with a fibrous capsule. The left lung contained a few conglomerate tubercles. There were tuberculous ulcers in the ileum and tuberculous peritonitis.

Diagnosis: Chronic pulmonary tuberculosis, with excavation, tuberculous pneumonia, moderate fibrosis and conglomerate tubercles in one lung; tuberculous enteritis and peritonitis. There was a caseous calcified focus of first infection within the pleura.

10: Female, colored, aged 29 years. She had worked until 2 weeks before confinement, and tuberculous symptoms appeared following delivery, 9 months before death, with cough and weakness.

Autopsy: Most of the left lung was covered by a dense pleura, and the parenchyma of the entire lung was consolidated and partly caseous, with some fibrosis in the upper lobe, and extensive excavation, the larger cavities at the apex having smooth firm walls, and the smaller ones scattered throughout the lung necrotic walls. There was a very large smooth-walled cavity in the right upper lobe and smaller ones nearby with necrotic walls; there was scant fibrous tissue at the apex and the rest of the lobe was firmly consolidated. There was extensive consolidation and several smooth-walled cavities in the middle and lower lobes. The lymph nodes in the right hilum contained caseous encapsulated nodules. There were tubercles in the liver.

Diagnosis: Chronic pulmonary tuberculosis, with advanced excavation, caseous pneumonia with consolidation of the greater part of both lungs, and scant fibrosis; tubercles in the liver. There were caseous encapsulated foci of a first infection in hilum lymph nodes.

11: Male, colored, aged 35 years. His illness began 5 months before death with "swollen stomach," cough, expectoration and night-sweats.

Autopsy: The upper half of the right upper lobe was covered by thickened pleura; the greater part of the lobe was occupied by a large cavity with well-organized wall; the rest of the lung was firmly consolidated and caseous, with a cavity in the middle lobe and a small area of air-containing tissue at the base of the lower lobe; about four-fifths of the left upper lobe was similarly affected. There was considerable fibrous tissue in both lungs. Near the right hilum in the lung substance there was a calcified (mortar-like) nodule, approximately 2 mm. across, and two nearby lymph nodes each contained a stony-hard nodule, one measuring 8 x 5 mm. and the other 3 mm. across; a lymph node beneath the bifurcation of the trachea contained a caseous lesion, 7 mm. across, with a thick fibrous capsule.

Diagnosis: Chronic pulmonary tuberculosis, with extensive excavation, moderate fibrosis and massive caseous pneumonia. There were calcified foci of first infection in lung and hilum lymph nodes and a caseous encapsulated focus in a tracheobronchial lymph node.

PLATE 2

Adult Type of Pulmonary Tuberculosis in Negro Adults (Continued)

12: Male, colored, aged 35 years. Symptoms appeared one month before death with a "cold;" he coughed and had three small haemorrhages.

Autopsy: At the right apex there was a fibrous and caseous lesion with small encapsulated, caseous foci. In the upper lobe were numerous conglomerate tubercles, and the lower lobe was partly consolidated with a tuberculous process. In the apex of the left lung there was a wedge-shaped mass of fibrous tissue surrounding a collapsed, smooth-walled cavity, 1.5 x 0.5 cm.; in the lower half of the upper lobe there were two consolidated areas, one extending along the interlobar fissure and the other along the outer margin; the rest of the lobe contained conglomerate tubercles; the lower lobe was thickly studded with conglomerate tubercles.

Diagnosis: Chronic pulmonary tuberculosis, with fibrocaseous lesion at each apex and cavity at the left, conglomerate tubercles in both lungs and moderately extensive tuberculous pneumonia.

13: Male, colored, aged 36 years. Symptoms began 13 months before death with cough and loss of weight.

Autopsy: A cavity occupied approximately one-third of the right upper lobe and a large part of the rest of the lobe was consolidated, caseous in places and with moderate fibrosis; there were small areas of caseous pneumonia in the middle and lower lobes. The entire left lung was consolidated, except for a

ADULT TYPE OF PULMONARY TUBERCULOSIS IN NEGRO ADULTS - Continued

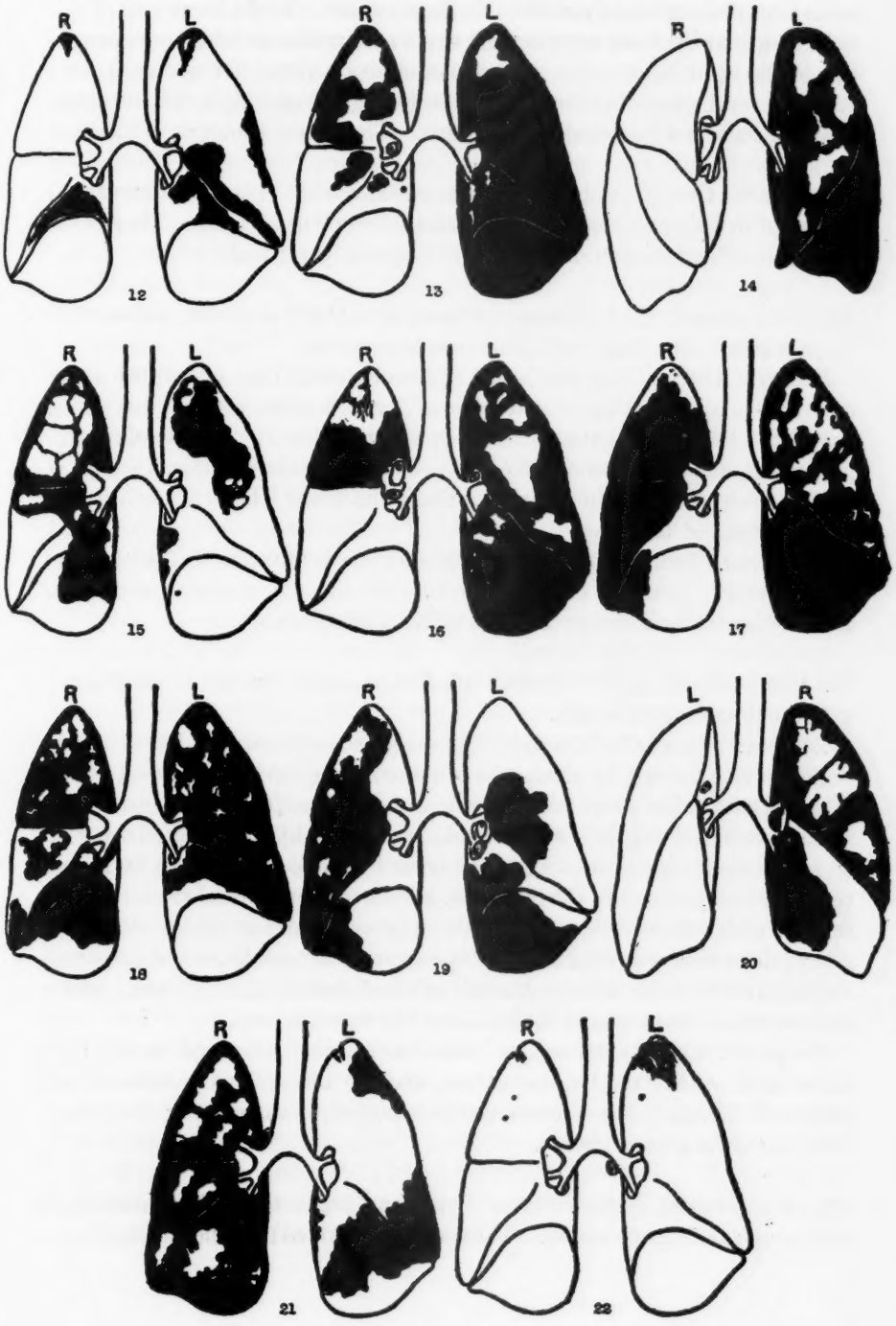


PLATE 2

large cavity with fairly smooth wall at the apex and several small ones in the lower lobe, and contained considerable fibrous tissue. In the lower lobe of the right lung near the inner margin there was a mortar-like nodule, 3 mm. across, and in the right hilum a lymph node containing a putty-like nodule, 1 mm. across; several spots of calcium were seen roentgenologically in the left upper lobe but could not be found on dissection. There were tuberculous ulcers in the ileum.

Diagnosis: Chronic pulmonary tuberculosis, with extensive excavation, advanced fibrosis and caseous pneumonia; tuberculous enteritis. There were caseous calcified foci of a first infection in lung and lymph node.

14: Male, colored, aged 37 years. Illness, of doubtful duration, was marked by pain in left side, cough and blood-streaked sputum.

Autopsy: The left lung was bound to the chest-wall throughout; the upper lobe was collapsed, owing to extensive cavity-formation, with the remaining tissue consolidated; the entire lower lobe was consolidated by patches of caseous pneumonia and conglomerate tubercles. There were a few scattered groups of conglomerate tubercles in the right middle and lower lobes. The liver and spleen contained tubercles.

Diagnosis: Chronic pulmonary tuberculosis, more advanced in the left lung, with extensive pleurisy, extensive excavation, massive caseous pneumonia, and conglomerate tubercles; tubercles of liver and spleen.

15: Male, colored, aged 37 years. His illness began 5 months before death with cough and loss of weight.

Autopsy: Almost all of the right upper lobe was replaced by a large smooth-walled cavity formed by numerous communicating cavities; the rest of the lobe was consolidated and fibrous tissue was abundant; there were two smaller smooth-walled cavities in the middle lobe surrounded by consolidated material, largely fibrous; almost one-half of the lower lobe was consolidated by fibrous tissue and caseation. In the left upper lobe there were several small irregular cavities with soft necrotic walls, considerable consolidation and scant fibrous tissue; there were tubercles undergoing caseation in both lobes and two pneumonic patches in the lower. A small calcified nodule, 2.5 x 1.5 mm., with a fibrous capsule was found in the left lower lobe near the base.

Diagnosis: Chronic pulmonary tuberculosis, most advanced in the right upper lobe, with extensive excavation, massive tuberculous pneumonia and advanced fibrosis. There was a calcified nodule, presumably of first infection, in the lung parenchyma.

16: Male, colored, aged 37 years. Symptoms began 6 months before death with cough and expectoration. The sputum contained tubercle bacilli.

Autopsy: The left lung was much heavier and more voluminous than the right; the pleura over the entire lung was thickened; the greater part of the upper lobe was replaced by ragged necrotic cavities; the rest of the lung was consolidated, and in large part caseous, and contained several irregularly shaped cavities. The right lung contained areas of consolidation sharply defined below by the interlobar line. A small cavity, 3 cm. across, was below the pleura at the apex, and was surrounded by fibrous tissue in which there were caseous spots. A bronchial lymph node at the hilum of the left upper lobe measured 1.8 cm. and contained a firmly calcified nodule, 3 x 1.5 mm.; below the left bronchus was a lymph node occupied by gray-white tissue in which there was perhaps caseation. A lymph node in the right hilum measured 3 x 1 cm. and contained a caseous nodule 1 x 0.6 cm., with a conspicuous capsule, 1 mm. in thickness; an adjacent lymph node was 1 cm. across and contained small encapsulated tubercles. There were tuberculous ulcers in the ileum and tubercles in the liver and spleen.

Diagnosis: Chronic pulmonary tuberculosis, with excavation, most advanced in left upper lobe, massive tuberculous pneumonia, and fibroid tuberculosis with cavity at right apex; tuberculous enteritis and tubercles in the liver and spleen. There were calcified, and caseous encapsulated foci, presumably of first infection, in tracheobronchial lymph nodes.

17: Male, colored, aged 38 years. Symptoms began 13 months before death, with cough followed by haemoptysis. The sputum contained tubercle bacilli.

Autopsy: The entire left upper lobe, except the anterior tip and the median surface of the lower half, was occupied by communicating cavities with fairly smooth walls, in which there were numerous dissected blood-vessels and scant fibrous tissue; the cavities were separated from the pleura by scarcely more than 2 to 3 mm. of thickened tissue; the tissue of the upper lobe not replaced by the cavities was consolidated largely by caseous material and some fibrous tissue; the greater part of the left lower lobe was consolidated, with confluent areas of caseation. The lower and median part of the upper lobe and the entire middle lobe of the right lung were almost homogeneously consolidated; at the extreme apex there was some air-containing tissue thickly studded with groups of caseous tubercles. A calcified focus was seen at the base of the left lower lobe in the roentgenogram but not found on dissection. There were tuberculous ulcers in the ileum and tubercles in the spleen and mesenteric lymph nodes.

Diagnosis: Chronic pulmonary tuberculosis, with excavation involving almost the entire left upper lobe, with scant fibrosis, massive tuberculous pneumonia of right upper and middle lobes; tuberculous enteritis, and tubercles of the spleen and mesenteric lymph nodes. There was X-ray evidence suggesting a calcified focus of first infection in the lung substance.

18: Male, colored, aged 38 years. Symptoms began three months before death with cough and hoarseness; the patient lost 25 lbs. in the last 2 months of illness.

Autopsy: The upper half of the right lung was covered by a thickened pleura; the parenchyma of the right upper lobe was replaced by numerous irregularly shaped cavities with smooth walls, by fibrous tissue and by areas of tuberculous pneumonia; similar but less advanced changes were found in the rest of the lung. The upper half of the left lung was covered by thickened pleura; the left upper lobe contained numerous cavities, some with well-organized walls and others with necrotic walls, and the rest of the lobe was consolidated by fibrous tissue and tuberculous pneumonia; the upper part of the lower lobe was consolidated. The X-ray plate suggested a calcified focus at the left apex, which could not be found on dissection. There was a single tuberculous ulcer of the appendix.

Diagnosis: Chronic pulmonary tuberculosis, with pleurisy, extensive excavation, massive tuberculous pneumonia and advanced fibrosis; tuberculous ulcer of the appendix. There was X-ray evidence suggesting a calcified focus of first infection in the lung substance.

19: Female, colored, aged 39 years. Illness began 7 months before death with cough and loss of weight. The sputum contained tubercle bacilli.

Autopsy: The greater part of the right lung except the extreme tip was consolidated and caseous, with abundant fibrous tissue; the anterior lappet of the upper lobe, together with the middle and lower lobes, contained several smooth-walled cavities surrounded by caseous consolidation. Large confluent areas of consolidation, in great part caseous, were found in the left upper lobe. The lowermost and posterior part of the lower lobe was occupied by caseous and gelatinous pneumonia. At the left hilum were two lymph nodes containing caseous encapsulated tubercles from 1.5 to 2 mm. in diameter. There was tuberculous perisplenitis, perihepatitis and tuberculous ulcers in the ileum.

Diagnosis: Chronic pulmonary tuberculosis, most advanced in the right lung, with excavation and moderate fibrosis, disseminated bronchogenic tuberculosis and tuberculous pneumonia; tuberculous enteritis, perihepatitis and perisplenitis. There were caseous encapsulated tubercles, presumably of a first infection, in bronchial lymph nodes.

20: Female, colored, aged 39 years. Symptoms began with tired feeling and weakness 8 months before death.

Autopsy: Dense adhesions bound both lungs to the chest-wall. There were two very large cavities in the right upper lobe, with moderate fibrous tissue, and one large and one small cavity in the middle lobe; the rest of these lobes and

nearly one-half of the lower lobe were consolidated. Conglomerate tubercles were numerous in the remaining air-containing tissue. A small lymph node within the left hilum above the bronchus to the upper lobe contained two small, firmly calcified nodules, measuring 1 mm. across, and 1.5 x 0.5 mm.

Diagnosis: Chronic pulmonary tuberculosis, with extensive excavation, massive consolidation and moderate fibrosis in one lung, conglomerate tubercles and extensive pleurisy of both lungs. There were calcified nodules of a first infection in a bronchial lymph node.

21: Female, colored, aged 42 years. Symptoms began one year before death with cough and loss of weight.

Autopsy: The entire right lung consisted of numerous cavities surrounded by dense bands of fibrous tissue, the remaining tissue being in large part caseous. Near the tip of the left apex there was a puckered area of thickened pleura, from which two bands of fibrous tissue penetrated the lung for a distance of 1.5 cm. In the same lung areas of caseous pneumonia were found near the apex, at the anterior tip of the upper lobe and in the lower lobe. In the lower lobe of the left lung just beneath the interlobar fissure and near the outer margin there was a firmly calcified encapsulated nodule, 4 x 2 mm., and to the right of the trachea a lymph node with a caseous encapsulated nodule.

Diagnosis: Chronic pulmonary tuberculosis, most advanced in the right lung, fibrous scar at left apex, massive tuberculous pneumonia with extensive excavation, advanced fibrosis. There were a calcified nodule of the lung and caseous encapsulated foci of first infection in a lymph node.

22: Male, colored, aged 49 years. He was admitted to the hospital in a comatose condition, suffering from gangrenous myositis and septicaemia; there was no history of symptoms referable to tuberculosis but physical signs were found at both apices.

Autopsy: The pleura was thickened over the left upper lobe and was bound to the chest-wall; section through the left apex revealed a small, smooth-walled collapsed cavity 3 x 10 mm. surrounded by dense fibrous tissue. Near the extreme apex of the right lung there was a puckered scar and nearby several spots of fibrous induration. In the left upper lobe there was a firmly calcified nodule, 2 mm. in diameter, and beneath the left bronchus a lymph node containing a small firmly calcified nodule; in the right upper lobe, just beneath the pleura and only 4 cm. apart, there were two firmly calcified encapsulated nodules, one measuring 2 mm. and one 3 mm.

Diagnosis: Pulmonary tuberculosis, with pleurisy, and with collapsed cavity and moderate fibrosis at left apex and a fibrous scar at the right apex. There were calcified foci of a first infection in lungs and lymph node.

PLATE 3

Childhood Type of Pulmonary Tuberculosis in Negro Adults

23: Male, colored, aged 17 years. Symptoms began 7 months before death with cough, expectoration and loss of weight. The sputum contained tubercle bacilli.

Autopsy: The upper two-thirds of the right upper lobe was air-containing, but the lower third was occupied by a cavity with necrotic wall, surrounded by caseous consolidation; there was massive caseous consolidation of the middle and lower lobes and numerous cavities with necrotic walls, of which the largest, measuring 5 cm. across, was situated in the lower half of the lower lobe; a lymph node, 3 cm. across, at the right hilum, was found to be caseous on section. Approximately one-third of the left upper lobe, including the apex, and the lower lobe were air-containing; the rest of the upper lobe was consolidated by a caseous process extending from the hilum toward the outer margin; a small lymph node in the left hilum contained a caseous area, 2 mm. in diameter. Tubercles were found in the liver, tuberculous ulcers in the ileum, and the appendix was tuberculous.

Diagnosis: Pulmonary tuberculosis of childhood type, with excavation, massive tuberculous pneumonia and caseation of hilum lymph nodes; tubercles in the liver, tuberculous appendix and tuberculous enteritis.

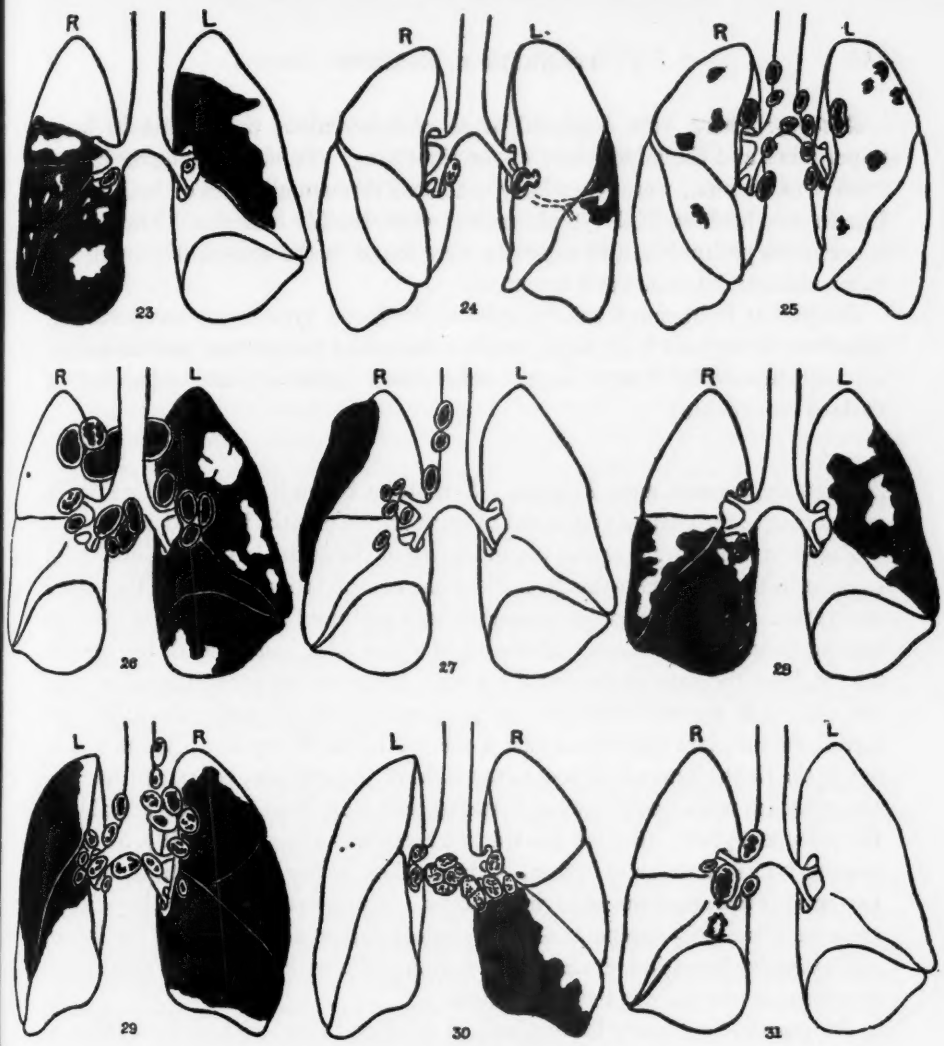
24: Male, colored, aged 19 years. His illness began 7 months before death with loss of weight and night-sweats; acute abdominal pain developed 3 weeks before death.

Autopsy: In the uppermost part of the left lower lobe there was a cavity, 1.5 cm. in diameter, surrounded by consolidated material, evidently caseous in part; the cavity was in communication with a medium-sized bronchial branch of the main bronchus to the lower lobe, and in the left hilum there was a lymph node, 1.5 cm. across, largely caseous and containing a small cavity; at one place the capsule of the caseous part of this node had broken through and there was a cavity in the contiguous lung substance. Below the right bronchus there was a lymph node, 2 x 1.5 cm., containing firm caseous areas measuring from 1.5 to 3 mm. across, some of which were conspicuously encapsulated. There was tuberculous peritonitis, and tuberculous ulcers were found in the ileum.

Diagnosis: Pulmonary tuberculosis of childhood type, with excavation and caseation of lung substance and caseation of lymph nodes, with rupture of the capsule of a caseous bronchial lymph node and cavity-formation in adjacent lung substance; tuberculous peritonitis and enteritis.

25: Female, colored, aged 20 years. Illness began 2 months before death with a "tight cold on the chest."

CHILDHOOD TYPE OF PULMONARY TUBERCULOSIS IN NEGRO ADULTS.



CHILDHOOD TYPE OF PULMONARY TUBERCULOSIS IN NEGRO ADULTS BEGINNING IN APEX OF THE LUNG

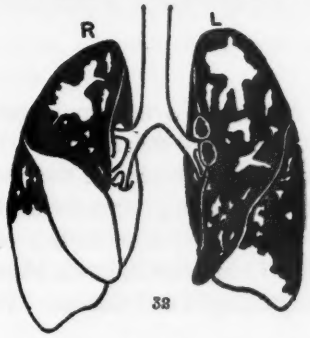


PLATE 3

Autopsy: There were scattered areas of tuberculous pneumonia in both upper lobes and the middle lobe of the right lung. Tubercles, ranging in size from 2 to 10 mm., were irregularly scattered through all lobes of both lungs. Eleven tracheobronchial lymph nodes were frankly caseous. There was tuberculous peritonitis, and tubercles were found in the spleen, liver, pericardium, kidneys, intestines and omentum.

Diagnosis: Pulmonary tuberculosis of childhood type, with conglomerate tubercles throughout both lungs, scant tuberculous pneumonia, and caseation of tracheobronchial lymph nodes; tuberculous peritonitis and tubercles in various other organs.

26: Female, colored, aged 22 years. Symptoms began 9 months before death with a cough; the patient continued to work until 6 months before death.

Autopsy: There was caseous consolidation of the entire left upper lobe, with cavities in the lower two-thirds, and similar consolidation of almost the entire lower lobe. Miliary tubercles were uniformly scattered throughout the air-containing tissue of both lungs. In the right upper lobe, just beneath the pleura, 2.5 cm. from the anterior border of the lung, there was an encapsulated caseous nodule, 2 mm. across, which did not resist cutting or grit under the knife, but contained sufficient calcium to cast a shadow in the X-ray film; lymph nodes, one in the right hilum and others to the right of the trachea, contained mortar-like granules within soft caseous material, and were readily distinguishable in the roentgenogram. Behind the trachea there was a huge mass, 10 x 5 cm., of caseous lymph nodes, and in front of the trachea, at the bifurcation, there were two smaller masses of caseous lymph nodes. There were general miliary tuberculosis and amyloid degeneration of the spleen; tuberculous ulcers in the ileum; and extensive caseation of mesenteric lymph nodes with sufficient calcification to appear at one place in the X-ray plate.

Diagnosis: Pulmonary tuberculosis of childhood type, with caseous tuberculous pneumonia with cavity-formation, massive caseation of tracheobronchial lymph nodes with beginning calcification, and caseous encapsulated nodule in lung; tuberculosis of ileum and mesenteric lymph nodes; general miliary tuberculosis.

27: Male, colored, aged 22 years. Symptoms began one year before death with cough, expectoration and loss of weight.

Autopsy: There was massive thickening of the pleura, with caseation and caseous consolidation of the underlying parenchyma, beginning close to the tip of the apex and extending along the outer surface of the upper lobe and the upper half of the middle lobe; lymph nodes in the hilum of the right lung and to the right of the trachea were enlarged and caseous. The intestines were matted

together and their peritoneal surface was studded with tubercles ranging in diameter from 3 to 10 mm. There was tuberculous perisplenitis.

Diagnosis: Pulmonary tuberculosis of childhood type, with localized tuberculosis of the pleura and underlying parenchyma, and massive caseation of adjacent tracheobronchial lymph nodes; tuberculous peritonitis, enteritis, and perisplenitis.

28: Female, colored, aged 23 years. Illness began 2 years before death, with weakness, cough and night-sweats. The sputum contained tubercle bacilli.

Autopsy: In the lower lobe of the right lung from the hilum to the base along the mesial margin, there were numerous cavities with fairly smooth but partly caseous walls, and the remaining tissue was consolidated and largely caseous, but with some fibrosis; part of the right middle lobe was similarly consolidated; at the right hilum there were two partly caseous lymph nodes, measuring 1.8 and 2 cm. In the lower two-thirds of the left upper lobe caseous consolidation, with a large smooth-walled cavity and a moderate amount of fibrous tissue, was found. There were caseous lymph nodes in the mesentery.

Diagnosis: Chronic progressive pulmonary tuberculosis of childhood type, with excavation, massive tuberculous pneumonia, some fibrosis, and caseation of bronchial and mesenteric lymph nodes.

29: Male, colored, aged 24 years. Symptoms began 3 months before death with a severe cold and persistent cough. Death was caused by perforation of a gastric ulcer and nontuberculous peritonitis.

Autopsy: There was massive tuberculous pneumonia involving the entire right upper lobe except the apex, the entire middle lobe and the whole of the lower lobe except the base; and there were conglomerate tubercles in the upper and lower lobes. Somewhat less than half of the left lung was consolidated and in part caseous. There were lymph nodes in the right hilum measuring from 2 to 3 cm. across and largely caseous, and a mass, 5 cm. across, above the right bronchus, also largely caseous; there were enlarged caseous lymph nodes in the left hilum, and to the right and left of the trachea and at its bifurcation.

Diagnosis: Pulmonary tuberculosis of childhood type, with massive tuberculous pneumonia of all lobes, conglomerate tubercles, and massive caseation of the tracheobronchial lymph nodes.

30: Male, colored, aged 32 years. Illness began one year before death, with cough, loss of weight and, later, hoarseness. No tubercle bacilli were found in the sputum.

Autopsy: Approximately two-thirds of the right lower lobe was consolidated and tough, and consisted of gray-black fibrous tissue intermingled with airless tissue of lighter gray color containing scattered spots of caseation. Through-

out the rest of both lungs there were firm gray nodules. Near the hilum of the right upper lobe there was a firm caseous focus, 6 x 7 mm., surrounded by strands of fibrous tissue; at the right hilum, in contact with the trachea and right and left bronchi, there were lymph nodes, forming below the bifurcation of the trachea a large mass thickly studded with gray nodules, some of which were caseous; in a lymph node in contact with the right bronchus there was a firmly calcified nodule, 3 mm. across. Below the costal surface of the left upper lobe there was a nodule, 2 mm. across, that gritted on section, and close by there was another larger, more firmly calcified nodule. Microscopic examination of the lung tissue showed numerous nodules, consisting of strands of concentrically arranged fibrous tissue that had undergone hyaline degeneration. These hyaline tubercles were occasionally bound together into groups by abundant fibrous tissue. There were a few fresh caseous tubercles formed largely by epithelioid cells. The greatly enlarged lymph nodes also contained fibroid hyaline tubercles and, in greater number, fresh tubercles with central caseation and surrounded by epithelioid, lymphoid and giant cells. There were several large areas of caseation surrounded by dense fibrous tissue.

Diagnosis: Chronic progressive pulmonary tuberculosis of childhood type, with fibrosis, caseation, and consolidation of the greater part of the right lower lobe, massive enlargement, fibrosis and caseation of adjacent tracheobronchial lymph nodes, healed hyaline tubercles. There were calcified nodules in lung parenchyma on one side and in bronchial lymph nodes on the other, probably the remains of a first infection.

31: Female, colored, aged 44 years. Illness began 6 months before death, with loss of weight and general failing in health. The patient was admitted to hospital in an unconscious condition.

Autopsy: The lower lobe of the right lung contained a cavity, approximately 2 cm. across, with a caseous wall, 1 to 1.5 mm. in thickness, and caseation extended into the adjacent lung tissue; in the right hilum there was a large mass of lymph nodes almost wholly caseous; at the lower part of this mass the capsule was ruptured and there was a softened but sharply circumscribed area about 1 cm. across extending into the lung substance. A branch of the pulmonary vein was in close contact with this secondary mass, and in the main branches of the vein three caseous tubercles, 1.5 mm., 2.5 mm. and 2 mm. in diameter, were seen projecting upon the intima and well separated from each other. There was a general miliary tuberculosis involving both lungs, the liver and other organs. Massive caseous tubercles were found in the spleen and kidneys and tuberculous ulcers in the ileum.

Diagnosis: Pulmonary tuberculosis of childhood type, with excavation, caseation of tracheobronchial lymph nodes, and general miliary tuberculosis; massive caseous tuberculosis of spleen and kidneys, tuberculous enteritis.

Childhood Type of Pulmonary Tuberculosis in Negro Adults Beginning in the Apex of the Lung

32: Female, colored, aged 17 years. Illness began a little over one year before death, with cough and blood-streaked sputum, which contained tubercle bacilli.

Autopsy: There was a large irregular cavity occupying about one-third of the right upper lobe and several smaller cavities distributed throughout the lobe; these cavities had ragged necrotic walls and the rest of the lobe was occupied by tuberculous consolidation in great part caseous; the upper part of the right lower lobe contained several cavities and the adjacent lung was consolidated and partly caseous. The left lung was voluminous and consolidated, save at the base, by tuberculous pneumonia; the apex of the upper lobe contained an irregularly shaped cavity with ragged wall, occupying about one-third of the lobe, and in the surrounding lung tissue there were bands of new fibrous tissue. In all lobes there were small cavities. The lymph nodes at the hilum of the left lung were large and succulent, containing abundant gray tissue. Two of these were 1 and 1.5 cm. across, respectively, and largely caseous. Above the left bronchus was a mass of lymph nodes, 4 x 3 cm., in large part gray and succulent, but not caseous. In the mesentery there were caseous lymph nodes with tough fibrous capsules, forming a mass 3 x 4 cm. In the caseous material, which was not gritty, there was some calcium demonstrated by the X-ray film. There were tuberculous ulcers in the ileum, tuberculous peritonitis and tuberculous laryngitis.

Diagnosis: Pulmonary tuberculosis with massive tuberculous pneumonia and multiple ulcerative cavities, beginning fibrosis, caseous tuberculosis of bronchial lymph nodes at left hilum with hyperplasia of tracheobronchial lymph nodes; tuberculous laryngitis; tuberculous enteritis and peritonitis, tuberculosis of mesenteric lymph nodes with encapsulation and beginning calcification.

PLATE 4

Childhood Type of Pulmonary Tuberculosis in Negro Adults Beginning in the Apex of the Lung (Continued)

33: Female, colored, aged 18 years. For 2 or 3 years the patient had a cough, which became severe 3 months before death; she was delivered four and a half months before death.

Autopsy: At the apex of the left lung there was a large cavity, and three smaller ones below it; the anterior lappet of the left upper lobe contained a large cavity and a group of small irregularly shaped cavities was found in the lower lobe; the tissue not destroyed by excavation was firmly consolidated; the cavities had smooth walls and there was a moderate amount of fibrous tissue in the upper lobe. At the left hilum there were lymph nodes containing caseous foci.

Throughout the right upper lobe there was massive caseous pneumonia with cavity-formation and some fibrosis; part of the right lower lobe was also consolidated; there were enlarged partly caseous lymph nodes at the hilum of the right upper lobe; beneath the right bronchus there was a lymph node with two caseous areas, 3 and 5 cm. across respectively, that were putty-like but did not grit when cut. The X-ray film showed that calcification was beginning. The mesenteric lymph nodes were enlarged and contained firm, caseous material that did not grit on cutting but cast a conspicuous shadow seen in the X-ray film. The largest of these spots was 1 cm. across. There were tuberculous ulcers of the ileum.

Diagnosis: Pulmonary tuberculosis of childhood type, with apical involvement, massive tuberculous pneumonia, excavation, and moderate fibrosis, caseation and beginning calcification of tracheobronchial and mesenteric lymph nodes, tuberculous enteritis.

34: Male, colored, aged 19 years. Symptoms began 4 months before death, with a "cold" and a persistent cough.

Autopsy: There was massive caseous pneumonia, involving most of the left lung; there was a moderate-sized cavity in the apex and several elsewhere; the cavities had necrotic walls. At the hilum of the left upper lobe there were three hyperplastic lymph nodes containing caseous areas, measuring from 2 to 5 mm. across. About two-thirds of the right upper lobe, about one-third of the middle, and one-half of the lower lobes were similarly consolidated, and the air-containing tissue was studded, fairly thickly, with conglomerate tubercles. There were scattered tubercles in the liver and an abscess, probably tuberculous, of the appendix.

Diagnosis: Pulmonary tuberculosis of childhood type, with apical involvement, massive tuberculous pneumonia of both lungs, excavation in one lung and conglomerate tubercles in the other, caseous tuberculosis of bronchial lymph nodes; tubercles in the liver and an abscess of the appendix.

35: Male, colored, aged 22 years. Illness began 6 months before death, with anorexia and loss of weight and strength. Cough developed later. Tubercle bacilli were found in the sputum.

Autopsy: The upper half of the right upper lobe was occupied by areas of caseous tuberculous pneumonia. A large part of the left upper lobe was replaced by very irregular cavities with necrotic walls, the largest of which was 10 cm. across, and the rest of the lobe was consolidated with tuberculous pneumonia; the left hilum contained lymph nodes ranging in size from 1.5 to 2 cm. across and largely caseous; below the left bronchus there was a lymph node, 3 cm. across, containing a caseous area, 1 cm. across. Tubercles were found in the liver and spleen, and tuberculous ulcers in the ileum. There was tuberculous peritonitis.

CHILDHOOD TYPE OF PULMONARY TUBERCULOSIS IN NEGRO ADULTS
BEGINNING IN THE APEX OF THE LUNG - Continued

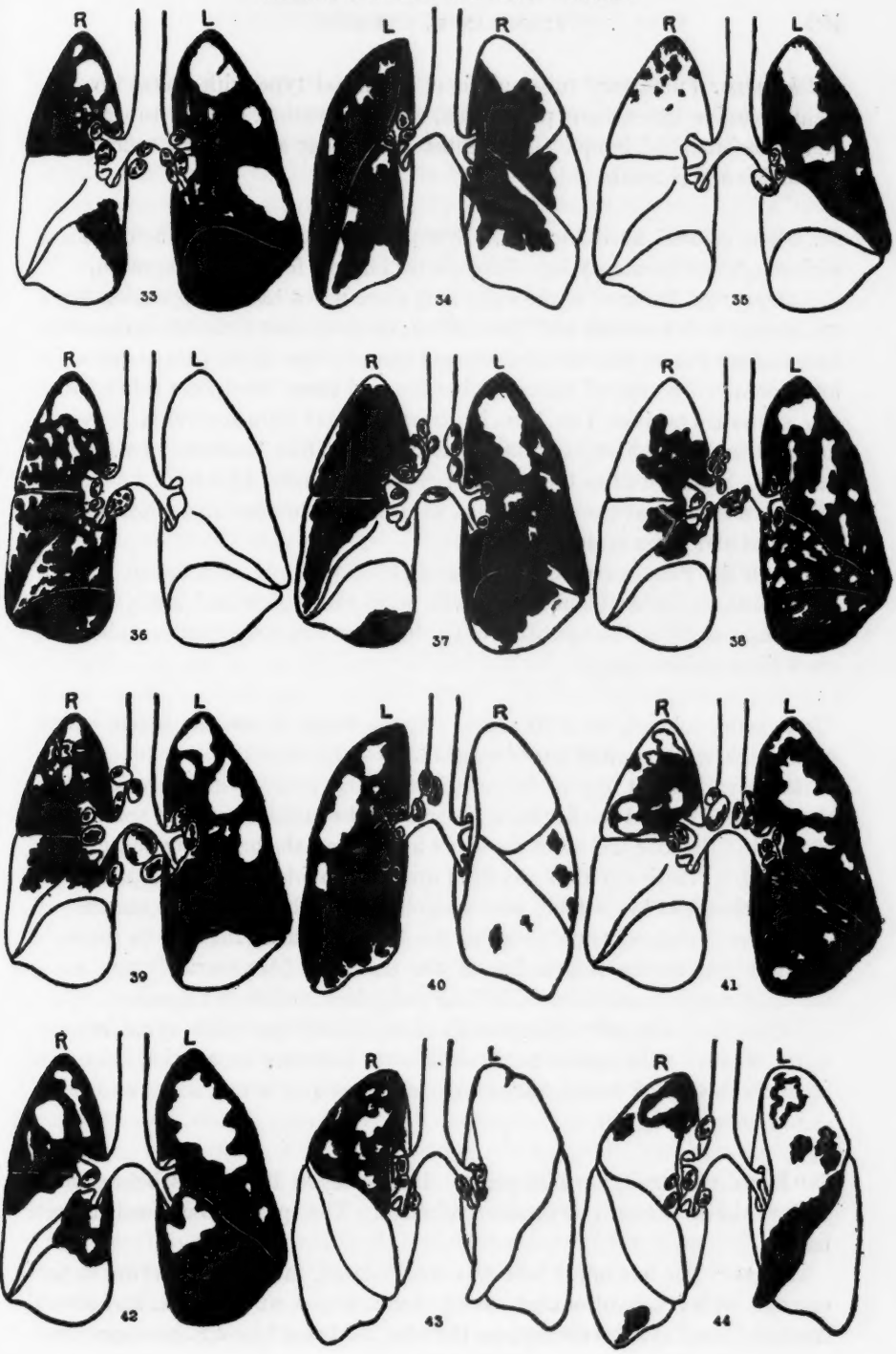


PLATE 4

Diagnosis: Pulmonary tuberculosis of childhood type with apical involvement, massive tuberculous pneumonia, with excavation, caseous tuberculosis of tracheobronchial lymph nodes; tubercles of liver and spleen, tuberculous peritonitis and enteritis.

36: Male, colored, aged 26 years. Symptoms began 19 months before death with cough and haemoptysis. Tubercle bacilli were found in the sputum.

Autopsy: At the apex of the right lung there was a cavity, approximately 4 cm. across, with a smooth wall 1 mm. thick; there was but little induration of the surrounding tissue; the rest of the upper lobe and the upper part of the lower lobe contained groups of caseous tubercles, and these lobes were riddled with smooth-walled cavities, 1 to 2 cm. in diameter; there were several large lymph nodes at the right hilum, containing caseous areas from 1 mm. to 1 cm. across; below the right bronchus there was a lymph-node mass, 3.5 x 1.5 x 2 cm., containing caseous areas from 2 to 5 mm. in size. There was tuberculosis of ribs, iliac joint and psoas muscle.

Diagnosis: Pulmonary tuberculosis of childhood type with apical involvement, massive tuberculous pneumonia with excavation and slight fibrosis, conglomerate tubercles, caseation of tracheobronchial lymph nodes; tuberculosis of ribs and iliac joint.

37: Female, colored, aged 26 years. Illness began 2 months before death, with cough, weakness and loss of weight (30 lbs. in 6 weeks).

Autopsy: The left upper lobe contained a large cavity with necrotic wall at the apex, and several smaller ones; the walls of the cavities were soft and ragged. The rest of the lobe and all of the lower lobe except the base were densely consolidated. Practically all of the right upper and middle lobes, and part of the base of the right lower lobe, were consolidated with tuberculous pneumonia. There were caseous lymph nodes at the hilum of each lung and to the right and left and at the bifurcation of the trachea. Mesenteric lymph nodes showed extensive caseation. The liver and spleen contained tubercles.

Diagnosis: Pulmonary tuberculosis of childhood type with apical involvement, massive tuberculous pneumonia with extensive excavation, caseation of tracheobronchial lymph nodes; caseous mesenteric lymph nodes and tubercles of liver and spleen.

38: Female, colored, aged 28 years. Illness began 10 months before death with weakness followed by productive cough. The sputum contained tubercle bacilli.

Autopsy: The left upper lobe was consolidated, in part gray-white, in part caseous, with a smooth-walled cavity, 5 cm. across, at the apex, and several large and small cavities throughout the lobe; the lower lobe was homogeneously

consolidated and riddled with smaller cavities; there was a moderate amount of fibrous tissue in the left lung; there were caseous lymph nodes in the left hilum. The right upper lobe contained great numbers of caseous tubercles in groups, within which small cavities had formed; in the upper part of the lower lobe there were numerous groups of tubercles. The lymph nodes at the right hilum and at the bifurcation of the trachea were caseous and above the right bronchus there was a large mass of lymph nodes, 3 cm. across, in large part caseous.

Diagnosis: Pulmonary tuberculosis of childhood type with apical involvement, massive tuberculous pneumonia with extensive excavation, conglomerate tubercles, moderate fibrosis, massive caseation of tracheobronchial lymph nodes.

39: Male, colored, aged 29 years. Illness began 11 months before death with cough, expectoration, loss of weight and finally severe hoarseness.

Autopsy: Both upper lobes contained large smooth-walled cavities with dense caseous consolidation of the remaining tissue, most advanced in the left lung; there was some new formation of fibrous tissue. About two-thirds of the left lower, about one-half of the right middle, and the hilum region of the right lower lobes were similarly consolidated and conglomerate tubercles were found in them. Lymph nodes within the hilum of each lung and at the bifurcation of the trachea showed extensive caseation. The ileum contained tuberculous ulcers and the mesenteric lymph nodes were caseous.

Diagnosis: Pulmonary tuberculosis of childhood type with apical involvement, extensive excavation, moderate fibrosis, conglomerate tubercles, extensive caseation of tracheobronchial lymph nodes; tuberculous enteritis and caseous mesenteric lymph nodes.

40: Female, colored, aged 30 years. Symptoms began 6 months before death, with loss of weight and strength, and, soon afterward, cough.

Autopsy: The left pleural cavity was obliterated, and a dense pleurisy bound the lung to the chest-wall and the lobes to each other. The left upper lobe was occupied by several large smooth-walled cavities and the rest of the lobe was densely consolidated by caseous pneumonia, but contained small cavities; the process was most advanced in the left apex; the entire left lower lobe was similarly consolidated; caseated lymph nodes, ranging from 1 to 2 cm. in size, were found at the hilum of the left lung and to the left of the trachea posteriorly. There were several small areas of caseous pneumonia in the middle and lower lobes of the right lung, and all three lobes contained conglomerate tubercles. There were tuberculous ulcers in the small intestine and the mesenteric lymph nodes were caseous.

Diagnosis: Pulmonary tuberculosis of childhood type with apical involvement, extensive pleurisy, massive tuberculous pneumonia of left lung with ex-

tensive excavation, patches of tuberculous pneumonia and conglomerate tubercles in right lung, caseous tuberculosis of tracheobronchial lymph nodes; tuberculous enteritis and caseous mesenteric lymph nodes.

41: Male, colored, aged 32 years. No history could be obtained.

Autopsy: The right upper lobe contained several smooth-walled cavities ranging in size from 0.5 to 4 cm., and most of the remaining tissue was consolidated, with moderate fibrous-tissue formation; the middle and lower lobes contained many conglomerate tubercles; two lymph nodes at the hilum were in part caseous and fibrous. The upper lobe of the left lung was the site of large smooth-walled cavities and consolidation; the lower lobe was almost homogeneously consolidated and contained cavities. Lymph nodes at the hilum of each lung and on either side of the trachea contained caseous foci and tough fibrous tissue. There were large masses of caseous lymph nodes in the ileum and mesentery.

Diagnosis: Pulmonary tuberculosis of childhood type with apical involvement and excavation, conglomerate tubercles, caseous tuberculosis and fibrosis of tracheobronchial lymph nodes; tuberculous enteritis and caseous mesenteric lymph nodes.

42: Male, colored, aged 39 years. Illness began 7 months before death, with weakness, loss of weight, night-sweats and shortness of breath. The sputum contained tubercle bacilli.

Autopsy: The pleura over the right apex was thickened, and beneath this there were numerous small irregular cavities with necrotic walls and surrounding consolidation; in the upper part of the right lower lobe there was a cavity, 3 cm. across; the middle and lower lobes contained scattered groups of tubercles. There was a caseous area, 3 mm. across, in a lymph node in the right hilum. A large part of the left upper lobe was occupied by a cavity with an irregular necrotic wall; elsewhere in the lobe were smaller cavities, caseous consolidation and a slight amount of fibrous tissue; in the upper part of the lower lobe there was an irregular cavity with necrotic wall, and the rest of the lobe was consolidated by tuberculous pneumonia.

Diagnosis: Pulmonary tuberculosis of childhood type, with apical involvement, massive tuberculous pneumonia with extensive excavation and scant fibrosis; caseation of a bronchial lymph node.

43: Male, colored, aged 48 years. Symptoms began 9 months before death with weakness and, later, a productive cough. Tubercle bacilli were found in the sputum.

Autopsy: The upper lobe of the right lung was extensively occupied by regular smooth-walled cavities; the tissue about the cavities was indurated, black

and airless; the lower lobe contained numerous gray tubercles, 2 to 3 cm. across, which showed some caseation. At the apex of the left lung there was a puckered scar penetrating 3 cm. into the parenchyma; groups of tubercles were scattered throughout the rest of the lung; at each hilum there was a mass of lymph nodes containing firm caseous patches, of which the largest was 1 cm. across. There were tuberculous ulcers in the ileum.

Diagnosis: Pulmonary tuberculosis of childhood type, with apical involvement on right side and fibrous apical scar on left, moderately extensive tuberculous pneumonia with excavation, moderate fibrosis, conglomerate tubercles, caseation of bronchial lymph nodes; tuberculous enteritis.

44: Female, colored, aged 54 years. Illness began with a cough 7 months before death.

Autopsy: There was caseous consolidation, involving about one-third of the left upper lobe and most extensive in the anterior lappet; a cavity in the apex measured 3.5 cm. across, and was surrounded by scant fibrous tissue. There was caseous consolidation of the upper third of the right upper lobe, with scant fibrous tissue, and an apical cavity with smooth but thin walls, and a patch of pneumonic consolidation in the lower lobe. There were three caseous lymph nodes in the right hilum and another beside the trachea. Beneath the right bronchus there was a lymph node containing numerous small stony-hard nodules and a mass measuring 8 x 5 mm., consisting of calcified particles from 1 to 2 mm. in size within a capsule 0.5 mm. in thickness. Groups of conglomerate tubercles were scattered in all lobes of both lungs. There were tuberculous ulcers in the ileum.

Diagnosis: Tuberculosis of childhood type with apical involvement, excavation at both apices, moderate tuberculous pneumonia, scant fibrous tissue, conglomerate tubercles in both lungs, and caseous and calcified tuberculous foci of tracheobronchial lymph nodes; tuberculous enteritis. There were firmly calcified foci, presumably of first infection.

PLATE 5

Adult Type of Pulmonary Tuberculosis in White Adults

45: Female, white, aged 21 years. Illness began 25 months before death. The symptoms were cough, loss of weight, night-sweats and shortness of breath. The sputum was repeatedly shown to contain tubercle bacilli.

Autopsy: The entire left lung contained numerous cavities, some with smooth firm walls and others with necrotic ragged walls, and was consolidated, mainly by caseous material; there was a moderate amount of fibrous tissue at the left apex. There were extensive areas of caseous consolidation in the right lung, involving all lobes, but most advanced in the upper part of the upper

lobe. What appeared to be a calcified nodule was shown roentgenographically in the left lung and another in the adjacent lymph node, but they were not found by dissection.

Diagnosis: Chronic pulmonary tuberculosis, with extensive caseation of both lungs, with excavation and moderate fibrosis throughout the left. Evidence of a first infection was seen roentgenologically in the lung substance and lymph node.

46: Female, white, aged 21 years. Illness lasted for 3 years before death, with cough, expectoration, loss of weight, malaise and anorexia. She had spent 16 months in a sanatorium. The sputum contained tubercle bacilli.

Autopsy: The apex of the right lung contained a large cavity with an irregular but organized wall, and the rest of the upper lobe was densely consolidated with caseous material and some fibrous tissue; the greater part of the middle and lower lobes was consolidated with tuberculous pneumonia, and elsewhere they were studded with tubercles. A large cavity, 6 x 4 x 1.5 cm., occupied the left apex and there was another cavity, slightly smaller, near it; most of the upper lobe and parts of the lower lobe were densely consolidated by fibrous tissue and caseous material; there were conglomerate tubercles in both lobes. Two roentgenographic shadows in the right hilum suggested calcified nodules in the lung and in a lymph node, but these were not found on dissection.

Diagnosis: Chronic pulmonary tuberculosis, with excavation at both apices, advanced fibrosis, tuberculous pneumonia, and conglomerate tubercles. There was roentgenographic evidence suggesting calcified lesions of a first infection in lung and lymph nodes.

47: Male, white, aged 22 years. Illness began 2 years before death, with cough, loss of weight and weakness.

Autopsy: There were extensive cavities with smooth walls, advanced fibrosis and small areas of tuberculous pneumonia in both upper lobes. In the upper part of the left lower lobe there was also a cavity surrounded by tuberculous pneumonic consolidation. Elsewhere in the lungs there were conglomerate tubercles. A focus of firmly calcified material was found in the right lower lobe and a calcified nodule in a lymph node at the right hilum; the mesentery contained three stony-hard nodules measuring 10, 7 and 3 mm.

Diagnosis: Chronic pulmonary tuberculosis, with advanced fibrosis, caseous pneumonia and excavation most extensive in the upper lobes, conglomerate tubercles in both lungs. There were calcified nodules, presumably of a first infection, in lung substance and bronchial lymph node, and in the mesentery.

48: Female, white, aged 24 years. Illness began 4 years and 6 months before death, with loss of weight and anorexia. The patient spent 2 years and 6 months in a sanatorium.

ADULT TYPE OF PULMONARY TUBERCULOSIS IN WHITE ADULTS

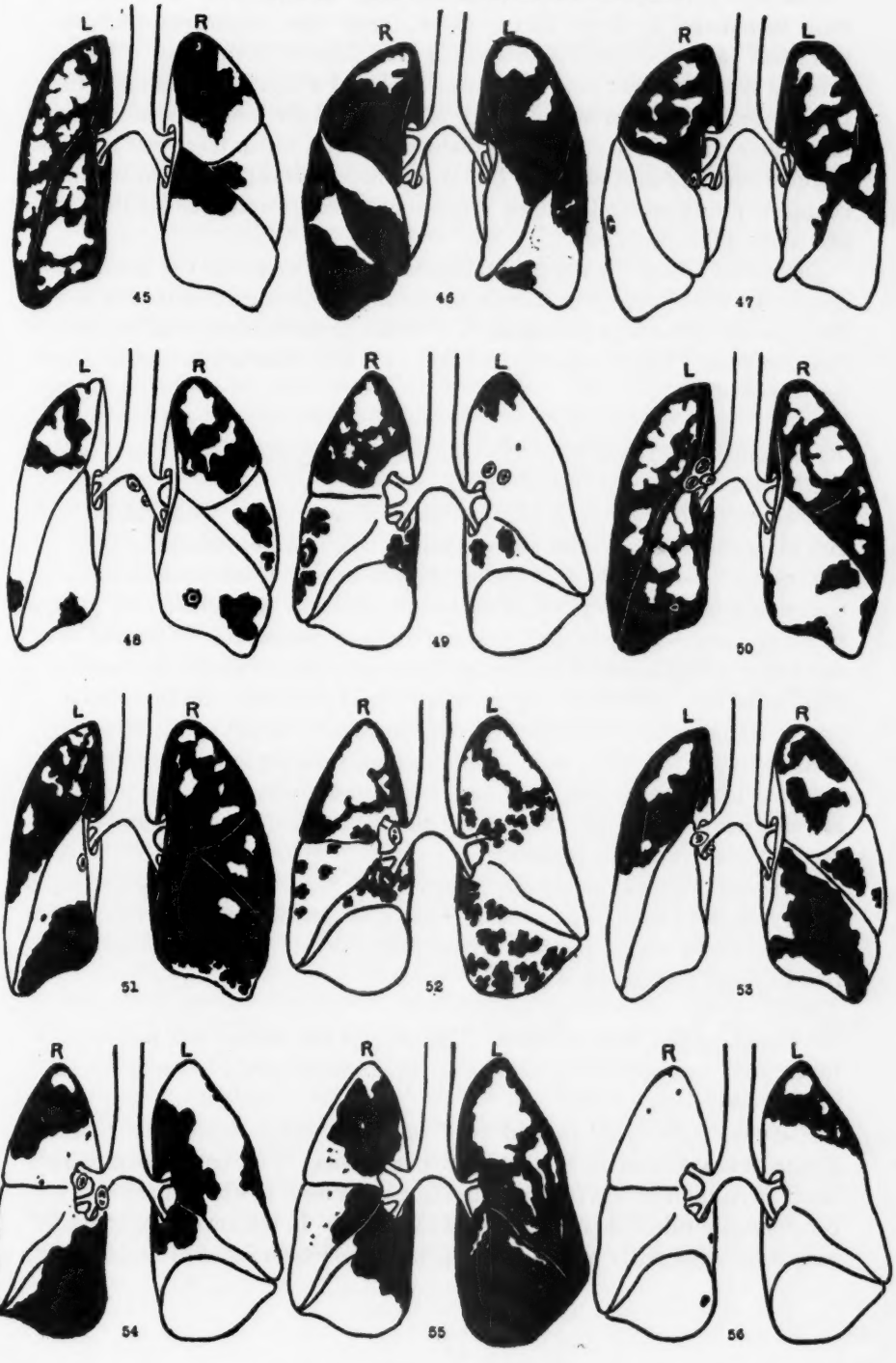


PLATE 5

Autopsy: Both upper lobes contained large cavities with well-organized walls surrounded by dense fibrous tissue; there were conglomerate tubercles and small patches of caseous pneumonia in all lobes of both lungs. Near the extreme apex of the left lung there was a puckered wedge of fibrous tissue infiltrating the parenchyma for a distance of 3 cm. In the lower lobe of the right lung, there was a cavity 9 mm. in diameter, within which there was a firmly calcified nodule, 3 mm. across. Two lymph nodes beneath the right bronchus contained firmly calcified nodules. Tuberculous ulcers were found in the ileum and tubercles in the spleen.

Diagnosis: Chronic pulmonary tuberculosis, with excavation at both apices and in the right lower lobe, advanced fibrosis, conglomerate tubercles and a few areas of tuberculous pneumonia in both lungs; tuberculous enteritis, tubercles of spleen. There were calcified foci of a first infection in the lung and lymph nodes.

49: Female, white, aged 29 years. Illness began 3 years and 8 months before death, with weakness and loss of weight and appetite.

Autopsy: The upper right lobe contained a large cavity with smooth wall and numerous small cavities surrounded by dense fibrous tissue involving all but the base and the hilum; in the middle lobe there was tuberculous bronchopneumonia and a small cavity; in the middle and lower lobes there were groups of conglomerate tubercles and areas of caseous pneumonia. The left apex was found to be caseous on section and there were patches of caseous consolidation in the left lower lobe. There was a round putty-like calcified nodule, 4 mm. in diameter, at the margin of the caseous area in the left apex, and a stony-hard nodule, 5 x 4 mm., in the left upper lobe; in the left hilum above the bronchus to the upper lobe there were two lymph nodes containing putty-like calcified nodules, 1.5 cm. x 0.75 cm. and 1.5 x 1 cm. The ileum and appendix contained tuberculous ulcers.

Diagnosis: Chronic pulmonary tuberculosis, most advanced in the right upper lobe, with caseous pneumonia, excavation and advanced fibrosis; tuberculosis of ileum and appendix. There were calcified nodules of a first infection in lungs and lymph nodes.

50: Female, white, aged 29 years. The patient was insane, and no history of tuberculous symptoms was obtained. Sputum contained tubercle bacilli 5 months before death.

Autopsy: Both lungs showed very extensive cavity-formation, advanced fibrous-tissue formation and caseous pneumonia. The only air-containing tissue in either lung was found in the right lower lobe, in which there were also conglomerate tubercles and patches of caseation. In the lower lobe of the left lung there was a gritty nodule, 4 mm. across; two lymph nodes at the left hilum

and one above the left bronchus contained calcified nodules, each about 4 mm. across.

Diagnosis: Chronic pulmonary tuberculosis, with extensive excavation, advanced fibrosis, caseous pneumonia and conglomerate tubercles. There were calcified foci of a first infection in lung substance and lymph nodes.

51: Male, white, aged 31 years. He was ill for 4 years and 2 months before death, with cough and progressive weakness.

Autopsy: At the tip of the left apex the pleura was densely thickened, and underlying this and throughout the upper half of the lobe there were several cavities surrounded by caseous consolidation, in which there was moderate fibrosis; all the air-containing tissue in this lung was in the lower third of the upper lobe and the upper two-thirds of the lower lobe; there was a large area of caseous consolidation at the base of the lower lobe. The right lung was entirely surrounded by adherent thickened pleura; on section the upper and middle lobes revealed numerous cavities, advanced fibrosis and caseous bronchopneumonia; the lower lobe was in large part consolidated and contained one cavity. A small stony-hard nodule, 3 mm. across, was found in the substance of the lower left lobe, 0.5 cm. beneath the pleura and near the interlobar fissure; a larger, firmly calcified nodule, 5 x 7 mm., was found in a lymph node beneath the left bronchus just as it entered the hilum of the lung. There were tuberculous ulcers in the ileum.

Diagnosis: Chronic pulmonary tuberculosis, with extensive excavation, advanced fibrosis, and caseous bronchopneumonia most advanced in the upper lobes; tuberculous enteritis. There were calcified nodules of a first infection in lung and lymph node.

52: Female, white, aged 35 years. Illness began 13 months before death with cough, loss of weight and night-sweats.

Autopsy: The right upper lobe was in large part replaced by a smooth-walled cavity, 8 cm. across. The middle and lower lobes contained patches of tuberculous bronchopneumonia, which were caseous at the periphery and fibroid in the centre. In the hilum region of the right lower lobe there were several small cavities surrounded by consolidated material, which was conspicuously fibrous. The left upper lobe contained two cavities with smooth fibrous walls, somewhat smaller than that at the right apex. The lung contained patches of tuberculous bronchopneumonia similar to those on the right side. A lymph node in contact with the bronchus to the upper right lobe contained several calcified foci. Tuberculous ulcers were found in the ileum.

Diagnosis: Chronic pulmonary tuberculosis, with excavation in both upper lobes, tuberculous bronchopneumonia with advanced fibrosis; tuberculous enteritis. There were calcified foci of a first infection in a bronchial lymph node.

53: Female, white, aged 36 years. Symptoms began two or three months before death, with pains in limbs and chest, cough and night-sweats. The sputum contained tubercle bacilli on two occasions.

Autopsy: There was a dense fibrous pleurisy over a considerable part of the left lung; in the upper half of the upper lobe there was caseation and two irregularly shaped cavities, one large and one small, with firm walls surrounded by dense fibrous tissue. In the apex of the right lung there was advanced fibrosis and an irregular cavity, 7 x 2.5 cm., with smooth wall; areas of tuberculous pneumonia were found in all three lobes, the largest occupying the greater part of the lower. Two firmly calcified nodules were observed in lymph nodes at the left hilum, the smaller beneath the bronchial branch to the lower lobe and the larger at the bifurcation of the bronchus. There were tuberculous ulcers in the ileum.

Diagnosis: Chronic pulmonary tuberculosis, with excavation and advanced fibrosis at both apices, fibrous pleurisy over one lung and extensive tuberculous bronchopneumonia in both; tuberculous enteritis. Bronchial lymph nodes contained calcified foci of a first infection.

54: Male, white, aged 38 years. Illness lasted 10 months before death, with cough and progressive weakness.

Autopsy: The right apex contained a cavity, 4 cm. across, surrounded by tough airless tissue, pigmented black and occupying approximately half of the upper lobe; most of the right lower lobe was indurated, black and airless, and contained several small cavities with smooth walls. The lung contained numerous firm gray nodules. The left lung was heavy, voluminous, tough and black, especially near the hilum, and in less solid parts it contained gray nodules. At the hilum of the right lung there were two lymph nodes containing caseous calcified material, and several calcified nodules of the right upper lobe were suggested in the X-ray plate. The right kidney had been removed. There was tuberculosis of the right adrenal gland. Microscopical examination of the lung showed anthracosis, fibrous induration and scattered, partially caseous tubercles.

Diagnosis: Anthracosis with chronic pulmonary tuberculosis and excavation at the right apex. There were calcified nodules of a first infection in bronchial lymph nodes and indicated roentgenographically in the lung substance.

55: Male, white, aged 39 years. He was ill for 10 years before death with loss of weight and cough. His wife had died of tuberculosis 8 years before his death.

Autopsy: The left lung was entirely covered with thickened pleura; there was no air-containing tissue in this lung, but dense fibrous consolidation throughout, within which at the base were a few encapsulated caseous areas and many cavi-

ties with smooth thick walls, particularly numerous and large in the upper lobe. Thickened pleura covered the upper lobe of the right lung, and large areas in all three lobes were consolidated with fibrous and caseous material; the upper half of the upper lobe was a fibrous scar. Encapsulated caseous and calcified nodules were found in the right upper and middle lobes.

Diagnosis: Chronic pulmonary tuberculosis, involving all of the left lung and much of the right, with extensive pleurisy, extensive excavation, advanced fibrosis. There were encapsulated caseous and calcified nodules of a first infection in the parenchyma of one lung.

56: Male, white, aged 41 years. He had had cough; otherwise the recorded symptoms were referable to the cause of death, which was sarcoma of the humerus.

Autopsy: There was a consolidated, fibrous, anthracotic and caseous wedge with its base, measuring 4 x 2 cm., on the external aspect of the right lung at the extreme apex, projecting into the parenchyma for a distance of 1 cm. The left apex contained a large cavity, 5 cm. across, with an irregular but smooth wall, and several smaller cavities, all surrounded by caseous and fibrous consolidation involving the upper third of the lobe. The right upper lobe contained two firm encapsulated nodules, the larger being 4 mm. across; on the diaphragmatic surface of the right lung near the inner margin there was a stony-hard nodule, 7 x 5 mm., and another above it. In the X-ray plate there was a shadow suggesting a nodule in a hilum lymph node.

Diagnosis: Chronic pulmonary tuberculosis, involving both apices, and most advanced, with excavation and fibrosis, in the upper third of the left lung. There was evidence of a first infection in the lung substance and suggested roentgenologically at the hilum, presumably in a lymph node.

PLATE 6

Adult Type of Pulmonary Tuberculosis in White Adults (Continued)

57: Male, white, aged 44 years. He was admitted to the hospital in uraemic coma and died a short time later.

Autopsy: At the apex of the right lung there was a large smooth-walled cavity surrounded by a dense fibrous and caseous consolidation. Both lungs were thickly studded with groups of caseous tubercles, least abundant at the bases. In the upper part of the lower lobe there was a consolidated area formed by caseous tubercles and fibrous tissue. An X-ray plate suggested a calcified nodule in the right upper lobe and another in a lymph node in the right hilum. There was tuberculous meningitis and tubercles were found in the spleen.

Diagnosis: Chronic pulmonary tuberculosis, with apical excavation and fibrosis in one lung, and conglomerate tubercles in both; tuberculous meningitis

and tubercles in the spleen. There was roentgenographic evidence of a first infection in lung and hilum lymph node.

58: Female, white, aged 46 years. Illness began about 8 months before death, with symptoms of associated cardiac failure.

Autopsy: In the right apex there was a large cavity surrounded by dense consolidation consisting chiefly of fibrous tissue, in which there were calcified nodules; the outer margin of the middle lobe and the base of the lower lobe were consolidated by patches of tuberculous pneumonia. The left apex contained a large cavity and several small ones surrounded by dense fibrous tissue; the anterior lappet of the upper lobe and the lower part of the lower lobe were consolidated by tuberculous pneumonia. There was an encapsulated putty-like focus, 4 mm. across, in a lymph node in the right hilum; there were three firmly calcified nodules, the largest 1 cm. across, in the mesentery.

Diagnosis: Chronic pulmonary tuberculosis, with excavation and advanced fibrosis at both apices, and tuberculous pneumonia in all lobes of both lungs. There were calcified nodules, presumably of a first infection, in a bronchial lymph node, and in the mesenteric lymph nodes.

59: Male, white, aged 59 years. The patient died from carcinoma of the stomach, and information as to the duration of symptoms referable to the lungs is vague. He had been coughing and expectorating blood-streaked sputum for a long time.

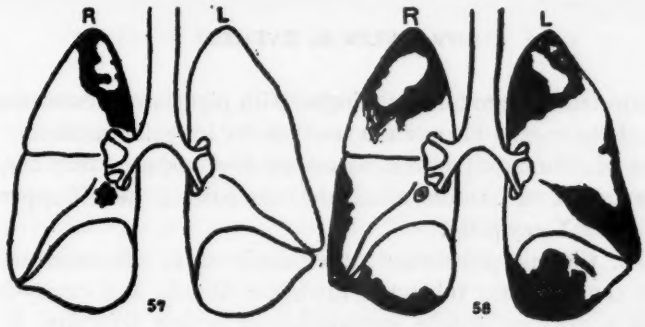
Autopsy: The left apex contained a fairly large cavity, measuring 5 x 3 cm., with dense fibrous and caseous material surrounding it and involving almost a third of the lobe. In the right apex there were four small, irregularly shaped cavities, surrounded by caseous material. There was a stony-hard nodule, 5 x 3 mm., in the left upper lobe, and another, 7 x 5 mm., in the right upper lobe; a lymph node at the right hilum contained a smaller calcified nodule. Tuberculous ulcers were found in the ileum.

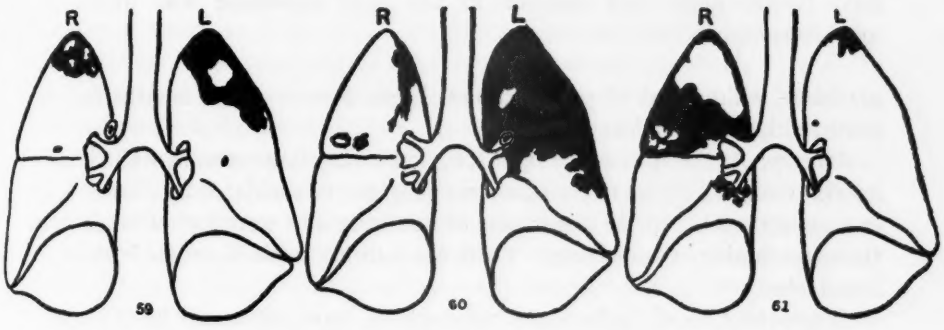
Diagnosis: Chronic pulmonary tuberculosis, with excavation and fibrosis at both apices, most advanced in the left; tuberculous enteritis. There were calcified nodules of a first infection in lungs and lymph node.

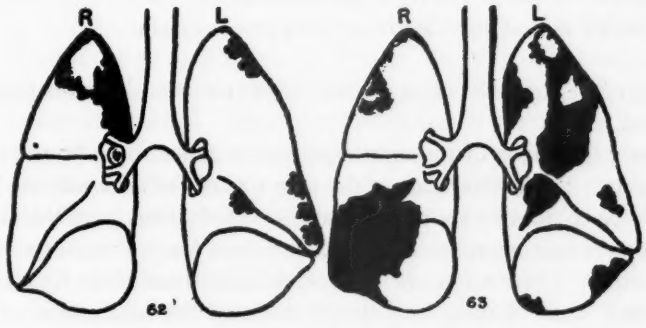
60: Female, white, aged 65 years. She was ill for 10 months before death, with cough, night-sweats and loss of weight.

Autopsy: At the apex of the right upper lobe, beginning within 1 cm. from the summit, there were caseous tubercles and strands of black fibrous tissue penetrating into the substance of the lobe as far as the interlobar border. In the anterior and lower part of the lobe there was a caseous focus containing a cavity 6 mm. across and another small caseous area near it. The upper two-thirds of the left upper lobe was in great part consolidated by confluent caseous

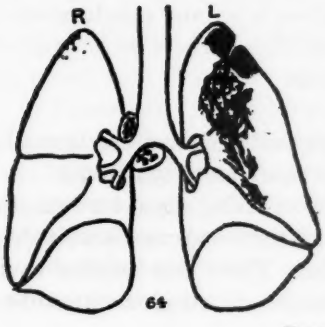
ADULT TYPE OF PULMONARY TUBERCULOSIS IN WHITE ADULTS - Continued







CHILDHOOD TYPE OF PULMONARY TUBERCULOSIS BEGINNING IN THE APEX IN A WHITE ADULT



CHILDHOOD TYPE OF PULMONARY TUBERCULOSIS IN A WHITE ADULT

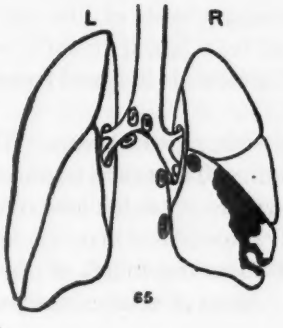


PLATE 6

nodules collected into groups and mingled with pigmented fibrous tissue, most abundant at the apex. There was a small cavity irregular in shape. A lymph node in the left hilum contained a caseous calcified nodule, 4 mm. across, and a calcified nodule, 2 mm. across, situated at the base of the left upper lobe was suggested in the X-ray plate.

Diagnosis: Chronic pulmonary tuberculosis, most advanced on the left side, with conglomerate tubercles, moderate fibrosis and cavity-formation. There was a calcified nodule, presumably of a first infection, in a bronchial lymph node, and another in the lung substance was indicated roentgenographically.

61: Male, white, aged 67 years. Illness began 3 years and 6 months before death, with cough and loss of weight.

Autopsy: At the apex of the right lung was a very large smooth-walled cavity and the greater part of the lobe remaining was consolidated by fibrous and caseous material. In the upper part of the lower lobe were foci of indurated tissue containing caseous spots. There was a firmly calcified nodule in the left upper lobe.

Diagnosis: Chronic pulmonary tuberculosis, most advanced in the right lung, with excavation at the right apex, and advanced fibrosis. There was a calcified nodule of first infection in the lung parenchyma.

62: Male, white, aged 68 years. Illness began one month before death, with a severe cold.

Autopsy: The apex of the right lung was occupied by a large cavity with smooth wall. The greater part of the lobe was densely consolidated by dense fibrous tissue containing spots of caseation. Both lungs were thickly studded with groups of caseous tubercles, which in places formed masses several centimetres across. There was a calcified nodule in the base of the right upper lobe, and another, much larger, in a lymph node at the bifurcation of the right bronchus within the right hilum. There were tuberculous ulcers in the ileum.

Diagnosis: Chronic pulmonary tuberculosis, with large smooth-walled cavity and advanced fibrosis of the right upper lobe, and conglomerate tubercles throughout both lungs; tuberculous enteritis. There were calcified nodules of a first infection in lung and lymph node.

63: Male, white, aged 70 years. The patient died from carcinoma in the floor of the mouth and there was no history of tuberculous symptoms.

Autopsy: The upper left lobe contained a cavity, about 6 x 3 cm., surrounded by densely consolidated material, in which there was considerable fibrous tissue, involving about one-fourth of the lobe. There was another cavity within the lobe. Areas of tuberculous pneumonia and conglomerate tubercles were

found throughout both lungs. The shadows of three calcified nodules in the left lung were detected by X-ray but not found by dissection.

Diagnosis: Chronic pulmonary tuberculosis, with excavation and moderate fibrosis in the left upper lobe, and patches of tuberculous pneumonia and conglomerate tubercles scattered throughout both lungs. There was roentgenological evidence of calcified foci of a first infection in the lung.

Tuberculosis of Childhood Type in White Adult Beginning in the Apex of the Lung

64: Male, white, aged 50 years. He died of endocarditis and cirrhosis of the liver and the duration of tuberculous symptoms was undetermined.

Autopsy: Along the external aspect of the right apex, 3 x 1 cm., reaching to the summit and penetrating into the lung about 1 cm., the tissue was tough, indurated and airless. Caseous spots occurred in this tissue. On the pleural surface of the right upper lobe there were numerous flat, gray and black nodules from 2 to 4 mm. across. There were dense adhesions over the left upper lobe. About 5 cm. from the extreme apex the pleura dipped deeply into the lung, and about it there was dense fibrous induration. Above and below this indentation of the pleura there were areas of tuberculous pneumonia with caseation, each about 5 cm. across. A great part of the remainder of the lobe was airless, indurated, and pigmented black, and contained spots of caseation and small irregularly shaped cavities with smooth lining. Above the right bronchus and beside the trachea was a much enlarged lymph node, 3 x 1.5 cm., in great part occupied by caseous material. Below the bifurcation of the trachea was a mass of lymph nodes containing four caseous spots, each about 0.5 cm. across. The X-ray film contained spots that may represent small calcified nodules, 1 and 2 mm. across, in the substance of the left lower lobe and a group of similar spots at the hilum of the left lung, but no calcified nodules were found on section of the lung. There was tuberculous meningitis.

Diagnosis: Chronic pulmonary tuberculosis, with advanced fibrosis and formation of small cavities; acute tuberculosis; tuberculous meningitis; caseous tuberculosis of tracheobronchial lymph nodes.

Tuberculosis of Childhood Type in a White Adult

65: Female, white, aged 27 years. Two years before death she had what was believed to be pneumonia lasting 4 weeks, and 6 months later her chest was tapped and about 48 ounces of turbid fluid was removed. Two months later the chest was tapped again with the same result. Four months before death two abscesses communicating with the pleural cavity appeared below the right breast and these ruptured, discharging foul pus.

Autopsy: The right lung, which was atelectatic but not consolidated, was collapsed and compressed against the mediastinum. Its surface was covered

by a layer of firm fibrin closely adherent to the pleura. The upper lobe was otherwise normal. The pleura of the costal surface of the lower lobe near its diaphragmatic border was perforated, and a sinus, with a wall of opaque caseous material, extended about 1 cm. into the lung substance. In a somewhat ill-defined area, 4.5 x 2 cm., extending from this sinus along the interlobar surface of the lower lobe, the tissue was airless and tough, and consisted of anthracotic fibrous tissue, in which there were spots of caseation, the largest 1 cm. across. Near the hilum of the lower lobe there were lymph nodes, from 1 to 1.5 cm. in length, containing conspicuous caseous foci, and in contact with the median border there was a lymph node 1.2 x 0.6 cm., which was almost homogeneously caseous. The left lung was voluminous. Upon the surface there were remains of old organized adhesions. The lowermost part of the upper lobe near the hilum and the upper half of the lower lobe contained numerous groups of caseous tubercles. The rest of the lung was air-containing and appeared to be normal. Several lymph nodes in contact with the left bronchus, and at the bifurcation of the trachea, contained caseous foci. In roentgenographic films there was no evidence of calcified lesions of preceding infection.

Diagnosis: Pulmonary tuberculosis of childhood type, with caseation and fibrosis of right lower lobe, caseation of adjacent lymph nodes, a sinus penetrating into pleural cavity with empyema necessitatus and collapse of the lung, conglomerate tubercles in the left lung and caseation of adjacent tracheobronchial lymph nodes.

THE COMPARATIVE SENSITIVENESS OF THE PIRQUET AND THE INTRACUTANEOUS TUBERCULIN TESTS[1]

JOSEPH D. ARONSON, DAVID ZACKS AND J. J. POUTAS

There has long been considerable uncertainty concerning the relative sensitiveness of the Pirquet and the intracutaneous tuberculin tests as a measure of the incidence of tuberculous infection. A positive reaction indicates only that infection with tubercle bacilli has occurred; whether the infection has been or will be followed by manifest disease is not indicated by the reaction alone. Upon the relative exactness of the two common methods of carrying out the tuberculin tests depends very largely the relative accuracy of statistical and other studies of tuberculous infection, and also, to a certain extent, the relative efficiency of case-finding procedures.

Pirquet (1) says that his method is less sensitive than either the local subcutaneous (*Stichreaktion*) or the intracutaneous test. Monti (2) noted that, of a group of 316 clinically nontuberculous persons, 50 per cent reacted to the Pirquet test and 59 per cent to the injection into the skin of 0.01 mgm. tuberculin, while 6 per cent of 131 nontuberculous persons did not react to the Pirquet test but did react to 1.0 mgm. of tuberculin injected intracutaneously. Of 58 cases of clinically manifest tuberculosis, 96.5 per cent reacted to both the Pirquet test and to the intracutaneous injection of 0.01 mgm. tuberculin. Of 263 patients tested by Veeder and Johnston (3), 10 per cent more gave positive reactions when the Pirquet test was followed by the intracutaneous injection of 0.01 and 0.1 mgm. tuberculin. Bass (4) tested a group of 206 children, ranging in age from less than one year to six years. He found that, whereas 10 per cent of the children reacted to the Pirquet test repeated three times, 25 per cent reacted to the intracutaneous test with 0.1 and 1.0 mgm. tuberculin. Happ and Casparis (5), in a series of cases of miliary tuber-

[1] The studies on which this paper is based were conducted under the auspices and with the support of the International Health Division of the Rockefeller Foundation and with the coöperation of the Henry Phipps Institute of the University of Pennsylvania and the Department of Public Health of Massachusetts.

culosis, found that the Pirquet test gave approximately the same percentage of positive reactions as intracutaneous injections of 0.01 mgm. tuberculin, but that, when the amount of tuberculin injected was increased to 0.1 and 1.0 mgm., 87.5 per cent of the patients gave a positive reaction as compared with 51.3 per cent who reacted to the Pirquet test.

Hamburger (6) says that the Pirquet test has an error as high as 40 per cent. Injecting 0.1 and 1.0 mgm. tuberculin, Krogsgaard (7) obtained positive reactions in 12 per cent more of the persons tested than with the Pirquet test. Rueda (8) found that, of 2,307 children up to the age of two years, 19.9 per cent reacted to the intracutaneous injection of 0.01 and 0.02 mgm. of tuberculin, but that of 1,475 children of the same age only 2.5 per cent reacted to the Pirquet test. Taillens (9) maintains that a higher percentage of young children react to the intracutaneous than to the Pirquet test, and concludes that their greater sensitivity to the former test is of a nonspecific character. Smith (10), in testing 3,112 children from less than one year to thirteen years of age, found that about 9 per cent more of them reacted to the intracutaneous than to the Pirquet test.

Under carefully controlled conditions Debré and Cofino (11) examined 132 babies up to the age of four years, who had been vaccinated with *BCG* and then placed in surroundings free from tuberculosis. These children were first tested by the Pirquet method, and those who failed to react were injected intracutaneously with 0.1 mgm. tuberculin; those who did not react to this dose were given a second injection of 0.5 mgm. and, if still negative, a third injection of 1.0 mgm. Individuals who failed to react to these tests were retested at irregular intervals as often as from seven to ten times. Of all these children, 42, or 31.8 per cent, reacted to the Pirquet test, and, of the 90 who remained negative, 75, or 83.3 per cent, gave positive reactions to the intracutaneous tests.

Heimbeck (12) states that 50 persons under 21 years of age who failed to react to the Pirquet test also failed to react when 1.0 mgm. tuberculin was injected intracutaneously. Slater and Jordan (13) compared the sensitiveness of the Pirquet and the intracutaneous tests with 0.1 mgm. tuberculin in a group of white children ranging in age from 6 to 18 years. He found that 4.2 per cent reacted to the intracutaneous but not to the Pirquet test, and that 2.8 per cent reacted to the Pirquet but not to the intracutaneous test. Esch (14) observed that guinea pigs inoculated with tubercle bacilli gave a positive reaction to the intracutaneous test nine days after infection but did not react to the Pirquet method at that time.

Lamy (15), who studied the time of appearance of the reactions in human beings, found that in four instances a positive intracutaneous reaction to 0.1 mgm. appeared in from 7 to 30 days before the Pirquet reaction was observed.

This brief review of the literature shows that the percentage of persons who react to the intracutaneous test and not to the Pirquet test has varied widely in the hands of different observers. This may be due in part to differences in the potency and amount of tuberculin used, in the time of reading and other details of technique, and in the selection of groups tested, such as regards age and history of contact with tubercle bacilli. Numerous such variables may be involved, as well as differences in the amount of tuberculin actually absorbed. With the intracutaneous method a definite quantity of tuberculin can be injected into the skin; with the Pirquet test, however, it is not known how much tuberculin is absorbed by the scarified skin.

In studies on the prevalence of tuberculous infection in school children of Philadelphia, Hetherington, McPhedran, Landis and Opie (16) found that the incidence of infection, as determined by means of the intracutaneous test with 0.01, 0.1 and 1.0 mgm. of tuberculin, was but slightly less than was observed by Hamburger and Monti (17) in Vienna some twenty years ago by means of the local subcutaneous tuberculin test (*Stichreaktion*). On the other hand, Chadwick and Zacks (18), using the Pirquet method, found considerably less tuberculous infection among school-children in Massachusetts than was found among those in Philadelphia.

To determine whether this discrepancy was due to a difference in the amount of tuberculous infection in the two communities or to a difference in the sensitiveness of the two methods, a comparative study was made of these tests with white inmates of an institution located in Waverley, Massachusetts, and with white children in schools near Boston.

The tuberculin used for the Pirquet method was the same as that used by Chadwick and Zacks (18) in Massachusetts and the tuberculin used for the intracutaneous test was the same as that used by Hetherington, McPhedran, Landis and Opie (16) in Philadelphia and by Aronson (19) in studies on the incidence of tuberculous infection in some of the rural communities of the South. Potency determinations of two samples of the tuberculin on tuberculous guinea pigs showed that that used for the Pirquet test was somewhat more potent than that used for the intracutaneous test.

The forearms of each person tested were washed with ethyl alcohol and the two tests were made simultaneously. A drop of undiluted Old Tuberculin was placed on the skin of the upper third of the forearm. Through this drop an area of epidermis, about 4 to 6 mm. in diameter, was removed by means of a platinum Pirquet scarifier, which had been previously flamed and cooled. Care was taken to avoid bleeding. On the opposite forearm 0.01 mgm. tuberculin in 0.1 cc. of sterile physiological salt solution was injected into the skin with a 1.0-cc. tuberculin syringe and a 26-gauge platinum needle one-half inch long. To prevent the removal of the tuberculin from the site of the Pirquet test the children were placed in small groups under the supervision of a nurse for 20 minutes.

The results of the two tests were observed after 48 hours and the positive reactions were recorded as + when there was an area of oedema not exceeding 10 mm. in diameter, ++ when the area of oedema measured from 10 to 15 mm. in diameter, +++ when it exceeded 15 mm., and ++++ when there was extensive oedema associated with necrosis. A reaction was considered negative when there were no redness and oedema at the site of injection. Those negative to the first Pirquet test were given a second test on the opposite forearm, and those negative to 0.01 mgm. tuberculin were retested with 1.0 mgm. tuberculin in 0.1 cc. of sterile physiological salt solution injected into the skin of the opposite forearm. The injection of 0.1 mgm. tuberculin was omitted because it had been found previously (19) that 1.0 mgm. could in most instances be injected into the skin of persons who failed to react to the smaller quantity without eliciting a severe reaction.

It was found that the slight or indefinite reaction produced in some cases by the Pirquet test could be verified only by repeating the test, whereas the slight or indefinite reaction produced occasionally by the intracutaneous test could be verified by the injection of the larger dose of tuberculin.

The results of the tests are presented in table 1.

It will be noted from table 1 that an average of 2.7 per cent and 3 per cent of all the children in groups 1 and 2 reacted to the injection into the skin of 0.01 mgm. tuberculin but not to the Pirquet test, and that an additional average of 19.2 per cent and 19 per cent of children in groups 1 and 2, respectively, reacted to the injection of 1.0 mgm. tuberculin.

From the data presented in table 1 it is evident that there is no mathematical factor that can convert the results obtained by one method into

those obtained by the other. Differences not readily explainable influence the percentage of reactions and make it impossible to devise a "correction figure" applicable to both tests.

It will also be noted in table 1 that the percentage of those who react to both tests is higher in the first group. A possible explanation is that 33 cases of manifest tuberculosis were found among this group. However, the number of cases of manifest tuberculosis in the families of the

TABLE 1

Comparison of the Pirquet and intracutaneous tuberculin tests in white children

AGE IN YEARS	NUMBER TESTED	TOTAL POSITIVE TO PIRQUET TEST		POSITIVE TO INTRACUTANEOUS INJECTION OF 0.01 MGM. O.T.		NEGATIVE TO PIRQUET TEST BUT POSITIVE TO INJECTION OF 0.01 MGM. O.T.		POSITIVE TO INTRACUTANEOUS INJECTION OF 1.0 MGM. O.T.		TOTAL POSITIVE TO INTRACUTANEOUS TEST		TOTAL NEGATIVE TO PIRQUET TEST BUT POSITIVE TO INTRACUTANEOUS TEST	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Group 1; Waverley, Massachusetts													
5–9	56	12	21.4	14	25.0	2	3.6	8	14.2	22	39.2	10	17.8
10–14	269	88	32.7	92	34.2	4	1.5	58	21.5	150	55.7	62	22.9
15–19	332	179	53.9	191	57.5	12	3.6	60	18.0	251	75.5	72	21.3
20–24	191	122	63.9	135	70.7	13	6.8	21	11.0	156	81.7	34	17.8
25–29	113	97	85.8	100	88.3	3	2.6	3	2.7	103	91.0	6	5.3
30–39	206	172	83.4	190	92.2	18	8.8	11	5.3	201	97.5	29	14.1
40–49	133	113	84.9	123	92.5	10	7.5	8	5.9	131	98.5	18	13.4
50+	69	56	81.1	58	84.1	2	2.9	8	11.6	66	96.0	10	14.5
Group 2: public schools near Boston													
5–9	1185	98	8.2	144	12.1	46	3.9	195	16.4	339	28.6	241	20.3
10–14	1197	234	19.5	264	22.0	30	2.5	234	19.5	498	41.6	264	22.0
15–19	260	85	32.7	89	34.2	4	1.5	74	28.4	163	62.6	78	30.0

school-children in group 2 was not determined during the course of this investigation.

The incidence of tuberculous infection in white school-children in Philadelphia, as determined with the intracutaneous test by Hetherington, McPhedran, Landis, and Opie (16), is compared in table 2A with the results obtained near Boston by the same method in this study. The results obtained with the Pirquet test near Boston and previously throughout Massachusetts by Chadwick and Zacks (18) are similarly compared in table 2B. It will be noted that, as shown by the intracutaneous test in both communities, there is considerably less infection in

the school-children in the vicinity of Boston than in those in Philadelphia. However, this discrepancy is much less than appeared in comparing the results of the intracutaneous test in Philadelphia with those formerly obtained with the Pirquet test in Massachusetts. Furthermore, the incidence of infection in the school-children near Boston, as shown by the Pirquet test, is about half that previously found by the same method throughout Massachusetts. The incidence of infection in Waverley, as indicated by the Pirquet test, is similar to that throughout the state,

TABLE 2A

Results of surveys with the intracutaneous tuberculin test in Philadelphia and in the vicinity of Boston

AGE IN YEARS	SCHOOLS IN PHILADELPHIA			SCHOOLS NEAR BOSTON			INSTITUTION AT WAVERLEY, MASSACHUSETTS		
	Number tested	Total positive		Number tested	Total positive		Number tested	Total positive	
		Number	Per cent		Number	Per cent		Number	Per cent
5–9	446	228	51.1	1,185	339	28.5	56	22	39.4
10–14	904	664	73.4	1,197	498	41.5	269	150	55.7
15–19	1,235	1,019	82.5	260	163	62.6	332	251	75.5

TABLE 2B

Results of surveys with the Pirquet tuberculin test throughout Massachusetts and in the vicinity of Boston

AGE IN YEARS	SCHOOLS IN MASSACHUSETTS			SCHOOLS NEAR BOSTON			INSTITUTION AT WAVERLEY, MASSACHUSETTS		
	Number tested	Total positive		Number tested	Total positive		Number tested	Total positive	
		Number	Per cent		Number	Per cent		Number	Per cent
5–9	16,066	3,687	22.9	1,185	98	8.2	56	12	21.4
10–14	24,085	7,388	30.6	1,197	234	19.5	269	88	32.7

but, as indicated by the intracutaneous test, it is closer to that found in Philadelphia. However, this institutional group is not truly comparable with the other groups consisting of school-children, because of the difference in environment, and because the history of contact is definitely known only with the institution.

It has been asserted by various investigators that a larger percentage of positive reactions may be obtained with the Pirquet test when it is repeated. Nothmann (20) found that, of 263 children, 47 per cent reacted to the first Pirquet test and 65 per cent reacted when the test was repeated. Bass (4) noted that 3.3 per cent of the children tested

reacted to the first Pirquet test, 6.8 per cent reacted to a second test, and 10.1 per cent reacted when the test was repeated the third time. Gittings and Donnelly (21) found that 6.5 per cent more of those tested reacted to the second Pirquet test than to the first. Heimbeck, however, found (12) that but 0.8 per cent more reacted to the second Pirquet test than to the first.

To corroborate the results obtained with the Pirquet test and to determine whether a greater number of positive reactions would be obtained, all of those who failed to react to the first Pirquet test were retested by the same technique on the opposite forearm. The results of these two tests are presented in table 3.

TABLE 3

Results of retest with Pirquet method

AGE IN YEARS	INSTITUTION IN WAVERLEY					PUBLIC SCHOOL NEAR BOSTON					TOTAL OF SCHOOLS NEAR BOSTON				
	Number tested	Positive to first test		Positive to second test		Number tested	Positive to first test		Positive to second test		Number tested	Positive to first test		Positive to second test	
		Number	Per cent	Number	Per cent		Number	Per cent	Number	Per cent		Number	Per cent	Number	Per cent
5–9	56	12	21.4	0	—	1,185	92	7.7	6	0.5	1,241	104	8.4	6	0.5
10–14	269	87	32.3	1	0.4	1,197	219	18.3	15	1.2	1,466	306	20.8	16	1.1
15–19	332	179	53.9	0	—	260	80	30.8	5	1.9	592	259	43.7	5	0.8
20–24	191	119	62.3	3	1.6						191	119	62.3	3	1.6
25–29	113	97	85.8	0	—						113	97	85.8	0	—
30–39	206	170	82.5	2	0.9						206	170	82.5	2	0.9
40–49	133	113	84.9	0	—						133	113	84.9	0	—
50+	69	56	81.1	0	—						69	56	81.1	0	—

It will be seen from this table that the percentage of those who reacted to the second Pirquet test, based on the total number examined, was only 0.8 per cent, an increment in conformity with the results obtained by Heimbeck (12).

SUMMARY

A study was made of the relative sensitiveness of the Pirquet and the intracutaneous tuberculin tests in determining the incidence of tuberculous infection. For this purpose two large groups of white persons near Boston were tested simultaneously by both methods.

Of children between the ages of 5 to 19 years who failed to react to the Pirquet test, from 1.5 to 3.9 per cent, with an average of 2.9 per cent,

reacted to 0.01 mgm. tuberculin. When 1.0 mgm. tuberculin was employed the total of those who failed to react to the Pirquet test but reacted to the intracutaneous test ranged from 14.2 to 28.4 per cent, with an average of 19.1 per cent. The total of those who reacted to the intracutaneous test and not to the Pirquet test yielded a negligible increase in the amount of infection detected by this means.

Of children between the ages of 5 and 19 years who failed to react to the Pirquet test, from 17.8 to 30 per cent, with an average of 22 per cent, reacted to the intracutaneous test with tuberculin. Repetition of the Pirquet test yielded a negligible increase in the amount of infection detected by this means.

These observations were compared with two previous surveys of white school-children, one made in Massachusetts with the Pirquet test (18), and the other made in Philadelphia (16) with the intracutaneous test, which showed a higher incidence of infection in Philadelphia. Children in schools near Boston were found to have tuberculous infection less frequently than public-school children in other parts of Massachusetts. In an institution near Boston the incidence of infection was higher than that of public-school children.

It was found that a mathematical factor, a "correction figure," could not be devised to convert results obtained by the one method into those obtained by the other.

The intracutaneous test is a practicable method for use in surveys, and can be carried out as expeditiously as the Pirquet test.

CONCLUSIONS

Thus, it was shown in a comparative study that the intracutaneous tuberculin test is more sensitive than the Pirquet test in determining the incidence of tuberculous infection, and that the results obtained by the two methods are not directly comparable.

REFERENCES

(1) PIRQUET, C.: Ergebn. d. inn. med. u. Kinderhk., 1910, v, 459.
(2) MONTI, R.: Wien. med. Wchnschr., 1912, lxii, 447.
(3) VEEDER, B. S., AND JOHNSTON, M. R.: Am. J. Dis. Child., 1915, ix, 478.
(4) BASS, M. H.: Ibid., 1918, xv, 313.
(5) HAPP, W. M., AND CASPARIS, H. R.: Ibid., 1922, xxiii, 527.
(6) HAMBURGER, F.: Ibid., 1922, xxiii, 481.
(7) KROGSGAARD, H. R.: Acta Paediatr., 1925, v, 103.
(8) RUEDA, P.: Arch. d. Méd. d. Enf., 1928, xxxi, 159.
(9) TAILLENS, J.: Bull. Soc. de Pédiat. de Paris 1929, xxvii, 286.

(10) SMITH, C. H.: Am. J. Dis. Child., 1929, xxxviii, 1137.
(11) DEBRÉ, R., AND COFINO, E.: Ann. l'Inst. Pasteur, 1930, xliv, 12.
(12) HEIMBECK, J.: Arch. Int. Med., 1931, xlvii, 901.
(13) SLATER, S. A., AND JORDAN, K.: Amer. Rev. Tuberc., 1932, xxv, 218.
(14) ESCH, P.: München. med. Wchnschr., 1914, lxi, 972.
(15) LAMY, M.: Bull. Soc. de Pédiat. de Paris, 1929, xxvii, 291.
(16) HETHERINGTON, H. W., MCPHEDRAN, F. M., LANDIS, H. R. M., AND OPIE, E. L.: Amer. Rev. Tuberc., 1929, xx, 421.
(17) HAMBURGER, F., AND MONTI, R.: München. med. Wchnschr., 1909, lvi, 449.
(18) CHADWICK, H. D., AND ZACKS, D.: New England J. Med., 1929, cc, 332.
(19) ARONSON, J. D.: Am. J. Hyg., 1931, xiv, 374.
(20) NOTHMANN, H.: Berl. klin. Wchnschr., 1910, xlvii, 381.
(21) GITTINGS, J. C., AND DONNELLY, J. D.: Arch. Pediatr., 1921, xxxviii, 78.

TUBERCULOSIS AND TUBERCULOUS INFECTION AMONG NURSES

A Study of the Nursing Personnel of the University of California Hospital[1, 2]

SIDNEY J. SHIPMAN AND ELIZABETH A. DAVIS

Nearly a decade ago an intensive study of the nursing personnel of the University of California Hospital was undertaken to determine the incidence of tuberculous infection and disease among the young women, and to investigate various related problems which might be expected to arise during the course of such a study. At this time the field was almost virginal. It was years later that we learned of the great interest of Jessamine S. Whitney in the subject, and of Johannes Heimbeck's work which was being carried out at the Municipal Hospital of Oslo, Norway. Since that time numerous investigators have become interested in the problem of tuberculosis among nurses and, in consequence, new viewpoints have been presented, viewpoints entirely different from those which seemed of importance to us at the time this work was undertaken. Nevertheless, the procedure in all of these studies has been essentially the same, consisting of family and past histories to determine contact and evidence of past tuberculosis, skin tests to establish infection or its absence, and physical and roentgen examinations for the purpose of detecting clinical tuberculosis as it arose.

The development of the present widespread study of this problem is interesting. Years ago Miss Whitney found, while making an analysis of tuberculosis mortality by age-groups, that the number of deaths from tuberculosis in general had declined 36 per cent in a decade, whereas the tuberculosis death-rate among individuals of 15 to 25 years of age had declined only half that amount. Moreover, there appeared a striking sex disparity. Said Miss Whitney (1) in 1928, "For the 15 to 19 group the death rate for girls is about 75 per cent higher than that for boys; and at the ages of 20 to 24 the women have a death rate 20 to 25 per cent higher than the men. This disparity has been visible in the United

[1] From the Department of Medicine, University of California Medical School, San Francisco, California.

[2] Read at the annual meeting of the American College of Physicians, San Francisco, California, April 4–8, 1932.

States figures since 1910, but the variations have become greater in recent years." Curiously, the exact reverse of this phenomenon seemed to be taking place in England and Wales, for Cobbett (2) of the University of Cambridge found the decline in tuberculosis mortality greatest between the ages of 15 and 25 and especially among young women. Here, then, was a problem of peculiar interest to us in the United States.

Limiting the study to nurses greatly narrowed the field. Largely because nurses could be easily followed, and, in addition, because certain peculiar problems of infection entered into a study of nursing personnel, statistics based upon such material began to make their appearance. Mücke (3) of the Eppendorf Hospital in 1926, in a study of 4,284 nurses and nuns, extending over a period of 27 years, reported 150 instances of clinical tuberculosis. Twelve of these patients died. Up to 1918 the incidence was one per cent, but following the war it rose to 4.6 per cent. Heimbeck (4) found that 12 per cent of student nurses developed some form of tuberculosis after entering training. He also made certain interesting observations, which will be mentioned later, concerning the incidence of disease among those who failed to react to tuberculin when they entered training.

At the University of California Hospital statistics are available from the class of 1922 to the present time. All of the prospective students have been carefully examined and the unfit weeded out. The remainder, the subjects of the present investigation, were regarded as healthy and evinced every likelihood of being able to finish training uneventfully.

The object of the present study, however, has not been merely the collection of data recording the incidence of clinically active tuberculosis, but has been an attempt by means of tuberculin tests, simultaneous roentgenograms and physical examinations to discover, as far as possible, the total incidence of infection, the degree of tuberculin hypersensitiveness, the accompanying roentgenographic changes, as well as those of physical examination, and to correlate the foregoing manifestations with those of clinical tuberculosis.

Ten years is a short time in which to observe significant changes in the history of tuberculous infection in the apparently healthy young adult; moreover, the material has been limited as to numbers, and in the earlier years records are incomplete; yet in the brief time which has elapsed since this study was begun interesting observations have come to light, observations which dovetail with the known facts of infection and disease as recorded experimentally by many workers.

FAMILY HISTORY

Table 1 summarizes the family histories of these individuals as regards tuberculous disease. Of a total of 30 individuals in 1925, three had positive family histories and 27 had no family tuberculosis, and so forth. Seventy-five per cent of the positive-family-history group reacted to intracutaneous tuberculin, while 25 per cent failed to react. Of the negative-family-history group 50 per cent reacted to tuberculin and 50 per cent failed to do so. In a preliminary report (5), covering classes to 1927 only, our statistics in this regard were at variance with the present figures. The latter, however, are what might be expected. Viewed in another light, of a total number of 84 positive tuberculin reactors (that is, individuals evidencing past contact with tuberculosis), 69, or 82.14 per cent, had negative family histories, while only 15, or 17.86 per cent, had positive family histories. Of 72 nurses with negative reactions, 67, or 90.3 per cent, had negative family histories, while 5, or 9.7 per cent, had positive family histories, showing, therefore, a failure to react to tuberculin in spite of known contact with tuberculous disease.

TABLE 1

Family history of students with respect to tuberculosis

YEAR	POSITIVE	NEGATIVE
1925	3	27
1926	4	36
1927	8	34
1928	4	31
1929	2	32
1930	6	36
1931	6	47
Total	33	243
Per cent	12	88

TUBERCULIN REACTIONS

Ten years after Pirquet and Schick's first publication on skin hypersensitiveness in man, Allen Krause pointed out how little definite information had come from studies made on such skin reactions. He remarked that it is at once plain that a study of this biological test as correlated with anatomical conditions could be made only rarely and in isolated instances. Further, it was only in individual and exceptional

cases that prolonged observation before infection, at the time of infection, and during the course of the disease could be carried out.

These statements are as true to-day as they were sixteen years ago. It has not been possible for us to test those girls before first infection; to do so certainly it would have been necessary to follow them from birth. However, it has been possible to find one group who reacted more or less violently to O.T. intracutaneously and another group who failed to react; furthermore, it has been possible to observe a certain small number of positive reactors who later failed to react to an identical dose, as well as a small number who became positive under observation.

Without going deeply into the significance of tuberculin hypersensitiveness as manifested by the skin reaction, it is, nevertheless, highly important in any study of this kind to constantly bear in mind certain fundamental principles or "laws," as Krause terms them when he stated (6):

1: There is no specific immunity without preëxisting tubercle.
2: Immunity first appears with the palpable development of the focus.
3: It diminishes with the healing of the focus.
4: It disappears with the enucleation of the focus.
5: The degree of immunity varies directly with the virulence of the immunizing microörganism, or, otherwise expressed, with the amount of tubercle and activity of lesion in the host. It is of the utmost significance that the circumstances of allergy exactly parallel those of specific immunity. As regards allergy we find that:

(1) It is never observed unless tubercle is present.
(2) It appears coincidently with the establishment of lesion.
(3) It diminishes as lesion heals.
(4) It varies directly with the intensity of the disease, which is in turn dependent, not wholly but in a large measure, on the virulence of the bacilli concerned.

Willis (7), who also quotes the above laws, observed the waning cutaneous allergy in infected guinea pigs as the infection subsided, but found that a high degree of allergy was immediately called forth by fresh reinfection. He also found that while cutaneous hypersensitiveness diminished with time (healing), this phenomenon could be elicited by larger and larger doses of tuberculin under the same experimental conditions.

Bearing in mind the foregoing facts, which are fundamental in the interpretation of any data based upon skin reactions in human beings as well as in animals, our findings may be briefly reviewed. Table 2 re-

cords the number of students tested, reactions elicited and the changes which occurred. These reactions were retested after a lapse of a year or more. A separate column shows those which were very strongly positive. All tests were made with 0.01 mgm. of O.T. intracutaneously, the dilutions having been made immediately before the testing was done. As for readings, a one-plus test was a slight but definite reaction with redness and induration measuring 1 x 1 cm. in diameter; a two-plus test, one measuring 2 x 2 cm. in diameter; and so on. Reactions less than 1 cm. without induration were classed as negative.

TABLE 2

Tuberculin reactions

	NEGATIVE	TOTAL POSITIVE	VERY STRONGLY POSITIVE (INCLUDED IN TOTAL POSITIVE GROUP)
Original	78 or 40%	96 or 60%	19 or 10%
Repeat	35 or 34%	68 or 66%	25 or 25%

Strongly positive to weakly positive	4
Weakly positive to strongly positive	5
Positive to negative	7
Negative to positive	19 (5 strongly positive)

Unchanged: negative 28; positive 50; strongly positive 15

Note in table 2 that while the percentage of positive reactors rose only slightly, the percentage of strong reactors increased much more markedly. The small totals are accounted for by the fact that tuberculin tests have been done routinely only since 1925 and, unfortunately, rechecks have not been available on all of these.

It is interesting to note that both Heimbeck and Geer (6) found that clinical tuberculosis developed more frequently among those who originally failed to react to tuberculin than among the original reactors. Our own figures show that the majority of the nurses who failed to react on entrance also failed to react when rechecked. While 28 remained negative, 19 became positive (5 strongly so) and 2 of these broke down with pulmonary tuberculosis. A third is now under suspicion on account of abdominal pain, fatigue and low-grade afternoon fever of 37.3 to 37.4°C.

Of the group who on entrance gave positive tuberculin reactions which later became more strongly positive (comprising five individuals), only one has developed clinical tuberculosis. Of the 15 persons who entered with strongly positive reactions, unchanged on recheck, 2 who originally

gave no evidence of clinical disease later showed physical signs and roentgen evidence of a pulmonary lesion. The remaining 7 cases of active disease since 1925 arose among the original moderate reactors to tuberculin whose reaction remained unaltered when repeated.

Those nurses whose reaction changed from strongly positive to a less marked reaction or from positive to negative without exception remained in good health.

ROENTGEN OBSERVATIONS

At the beginning of this study we were hopeful that successive chest films in conjunction with intracutaneous tuberculin tests might reveal significant relationships. We were interested in apical pleuritis, so called thickened interlobar septa, hilum calcification and the like. One of us, through personal contact with Van Zwaluwenburg, had become interested particularly in possible extension of lesion from the apical pleura to the lung, the assumed "coning" of this writer (7). Such extension of lesions from apical pleuritis to definite parenchymatous involvement was never observed in this series, although apical pleuritis as such was apparently about as common in our series as reported in Van Zwaluwenburg's original paper (between 30 and 40 per cent).

However, whether the visualization of the apical pleural shadow represents evidence of past tuberculous infection or whether under certain conditions the normal pleura may be so visualized, we are not sure; so with the other roentgen criteria which we adopted in the beginning. As the work progressed it became evident that few conclusions could be drawn or few relationships established from a comparison of the films and tuberculin reactions. This appeared true with one exception: namely, that students who were originally or who later became highly allergic would, if they developed clinical tuberculosis, show an exudative reaction, whereas those who reacted only moderately to tuberculin would develop productive or proliferative lesions if they developed clinical tuberculosis at all.[3] This observation seemed to us of the utmost importance and will be discussed more fully in connection with certain individual cases to follow.

[3] The meaning of the terms "exudative" and "productive or proliferative," as used in this connection, has been described in "The Type Treatment of Pulmonary Tuberculosis," *California and Western Medicine*, January, 1926. For a critical review of the subject, read "Modern Concepts in the Pathology of Tuberculosis," AMERICAN REVIEW OF TUBERCULOSIS, 1928, xvii, 601.

In our earlier paper the incidence of tuberculosis was computed as the percentage of the average annual enrollment in the school, represented by those individuals who developed lesions during each year. Bringing these figures up to date, we have the data shown in table 3.

TABLE 3

Annual incidence of clinical tuberculosis in the student body

YEAR	TOTAL NUMBER OF STUDENTS	NUMBER WHO DEVELOPED LESIONS
1922	122	2
1923	129	2
1924	137	1
1925	122	11
1926	130	1
1927	129	3
1928	120	0
1929	111	2
1930	111	1
1931	120	3
Total	1,240	26 or 2.18%
Average	124	2.6

We have also computed the incidence on the basis of the percentage of active disease arising in the course of the entire training period, thus including a three-year period for each student.

Under this classification, table 4 reveals a considerably higher rate.

TABLE 4

Incidence of tuberculosis for the period of training (three years)

CLASS	NUMBER OF STUDENTS	NUMBER WHO DEVELOPED LESIONS
1922	38	2
1923	37	2
1924	37	1
1925	38	11
1926	44	1
1927	29	3
1928	35	0
1929	34	2
1930	42	1
1931	53	3
Total	387	26 or 6.72%

Of this total of 26 cases in table 4, three showed roentgen evidence but no clinical manifestations of tuberculosis. X-rays showed improvement in subsequent films and no therapy was required. Hence, strictly speaking, these perhaps should not be included in our cases of tuberculous illness; and without them the incidence would be approximately an even 6 per cent.

Other figures are apparently somewhat conflicting. Britton and Bollmann in 1925 made the statement that 2.2 per cent of all nurses employed in Chicago had tuberculosis (8). Heimbeck's figures for student nurses over a four-year period were much higher (12 per cent). Geer (*loc. cit.*) found 5.5 per cent in a two-year period. The statistics of both Heimbeck and Geer, however, deal with nurses who have been abundantly exposed to tuberculous infection while working in tuberculosis wards.

To date, our students have not had a comparable contact. Beginning with the present year an affiliation with the San Francisco Hospital will give a limited period of duty on the tuberculosis wards at the latter institution. It will be enlightening to note whether the incidence of tuberculosis and the percentage of positive reactors to O. T. will show an increase.

The foregoing figures refer only to nurses who developed clinical tuberculosis while in training.

To discover what had occurred among those graduated from the University of California Nursing School during the past decade, a questionnaire was sent to all such graduates in February of this year. From a total of 374 alumni 330 replies were received. Thirteen of these had developed definite clinical tuberculosis. Three others had had unexplained fevers, cough, or some such difficulty, but without definite or conclusive evidence of tuberculous disease, and hence were not included in our figures.

Approximately four (3.94) per cent, therefore, of those who had escaped clinical tuberculosis while in training subsequently developed the disease. A list of these individuals and the type of lesion developed is presented in table 5.

TABLE 5

YEAR OF GRADUATION	NUMBER OF CASES	TYPE OF LESION
1922	3	(1) Apical lesion (2) Apical lesion (3) Pleurisy with effusion
1923	2	(1) Apical lesion (2) Apical lesion
1924	4	(1) Extensive pulmonary (2) Apical lesion (3) Apical lesion (4) Pleurisy with effusion
1925	1	(1) Pleurisy with effusion
1926	0	
1927	2	(1) Apical lesion (2) Spontaneous pneumothorax
1928	1	(1) Apical lesion
Total.....	13	

These cases in table 5, added to the 6 per cent which arose during training, bring the total incidence to about 10 per cent. Among the more recent graduates particularly we must undoubtedly expect the appearance of further tuberculous lesions. Thus we are confronted with a sufficiently large number of cases to constitute a serious problem.

It is cheering to note that only one of the graduates died following the development of frank lesion. This was the young woman of the class of 1924 who had extensive pulmonary tuberculosis at the time of discovery. Only two, both of whom are improving satisfactorily, are at present incapacitated. The remaining ten have recovered.

Of the students (26 in all), 14 subsequently completed their training and are now well, only one having had a second break in the interim. Six failed to return to training here. Of these, two have since graduated from other nursing schools, three others are known to be in good health, and with the sixth we have lost touch.

Six are at present incapacitated, but in no case has the disability existed for as long as a year and all are showing steady improvement.

Thus, while the morbidity statistics are rather high, the mortality of only one of the entire group is hopeful indeed.

The following list presents the interesting features of the students who broke down with various types of tuberculosis while in training.[4] Un-

[4] In the majority of the patients, lesions were discovered in the course of routine physical X-ray examinations, or in check-ups suggested on account of some minor complaint. Not a single student considered herself definitely ill and usually the presence of symptoms was conceded only on careful questioning.

fortunately, some of the records of earlier years were not as complete as those made later on and comparisons are, therefore, not always possible:

1922: (1) G. S. F. H. positive. Lesion right upper lobe, onset with haemoptysis. Left training. Present status unknown.

(2) R. K. F. H. negative. Lesion right apex. Underweight. Finished training without definite break. Now well.

1923: (1) E. C. F. H. negative. Postinfluenzal. Apical lesion. Finished training. Below par and under observation for some time. Well when last heard from.

1924: (1) V. G. F. H. negative. P. H.: Peritonitis with ascites, *aet.* 12, ill 6 weeks. During training definite pelvic tuberculosis, with tumor requiring surgical removal. Finished training. Well since operation.

1925: (1) H. A. F. H. positive. Exudative parenchymatous lesion both lungs. Left training and entered a sanatorium. Later developed intestinal tuberculosis. Recovered and has been well and active for four years.

(2) G. B. F. H. negative. Lesion of bronchial lymph nodes. On leave six months. Well since that time.

(3) H. J. F. H. negative. Pleurisy with effusion. Later parenchymal lesion. Left training. Later completed course in hospital in Arizona.

(4) E. K. F. H. positive. Lymphatic tuberculosis (bronchial lymph nodes). On leave six months. Returned and graduated. Now in good health.

(5) M. M. F. H. negative. Pleurisy with effusion. On leave 8 months, returned and finished training. Later break with parenchymatous lesion. Well at present.

(6) O. M. F. H. positive. Fibrinous pleurisy. Left training. Later completed at Santa Barbara. Continued underweight and with fatigability. Recent operation in 1931 for adenomata of thyroid, with much subsequent improvement of condition.

(7) J. R. F. H. negative. Small localized parenchymatous lesion. Six months' leave. Finished training and has continued in good health.

(8) M. T. F. H. positive. Lesion tracheobronchial lymph nodes. Left training. After a year's rest at home entered University and took degree with bacteriology major. Well now.

(In addition to the 8 patients listed, three, previously mentioned with X-ray evidence of lesion but no symptoms, are omitted.)

1926: (1) L. A. F. H. negative. P. E. negative. X-ray showed large amount of calcium in right hilum and left upper. Definite

parenchymatous lesion right upper, apparently old. O. T. 2 plus. One year later had pleural pain and slight fever one week. Off duty 2 weeks. P. E. showed râles low in left axilla. X-rays showed no change. The following year (two years after original) X-ray showed calcium as noted. Lesion in right upper in general more circumscribed and less in extent except for lobular exudative lesion, 1.5 cm. in diameter, below right clavicle. O. T. 4 plus. Put on four-hour duty (half-time) and X-rays checked at intervals. Improved; finished training. Well now.

1927: (1) C. R. F. H. negative. Underweight, fatigability, slight afternoon fever brought out on questioning because of X-ray findings. Proliferative lesion right upper. O. T. 2 plus. Cured in sanatorium. Now in good health.

(2) E. G. F. H. negative. P. H. and original X-ray negative. Two years later noted weight-loss, slight fatigue. P. E. negative. X-ray showed proliferative lesion both uppers. O. T. always 2 plus. Took the cure at home, finished training, now in good health.

(2) K. E. F. H. negative. Weight-loss, abdominal pain. Pelvic tuberculosis. O. T. originally 2 plus; repeat 1 plus. Took the cure at home. Now well.

1929: (1) R. G. F. H. negative. P. H. and P. E. negative. Original roentgenogram and tuberculin test negative in 1929. In April, 1931, O. T. test 5 plus. Roentgenogram revealed very questionable lesion above 2nd rib on left side. This developed into frank exudative lesion, with limited mobility and loss of vesicular murmur at left apex. Now taking cure at home.

(2) F. F. Negative family and past history. On physical examination in 1929 movement of left chest was less than right and there were a few fine crackles below left clavicle which disappeared on cough. At this time roentgenogram was essentially negative and O. T. 4 plus. When repeated in April, 1931, O. T. was 8 plus. Roentgen examination now revealed an exudative lesion in left apex. Took cure in a sanatorium. Condition now apparently arrested.

1930: (1) M. J. Negative family history, past history and physical examination. Original tuberculin test 3 plus. Roentgenogram negative. Developed tuberculous cervical adenopathy in spring of 1931, with fatigability and loss of weight with low-grade fever. Tuberculin test 10 plus. Resting at home, having quartz-lamp therapy. Gaining weight. Temperature normal.

1931: (1) C. McQ. Negative F. H. and P. H. P. E. negative except underweight. Tuberculin test 2 plus. Developed pleurisy with effusion in August, 1931. Skin reaction at this time unchanged. Has gained weight. Temperature normal. On active exercise.

(2) E. P. F. H. positive. P. H. negative. P. E. negative. Negative tuberculin test. Roentgenogram essentially negative. In February, 1932, developed fibrinous pleurisy on left side. Tuberculin test now 6 plus. Roentgenogram now reveals suspicious lesion in left 2nd interspace.

(3) O. J. Negative F. H., P. H., and P. E. as well as roentgenogram. Tuberculin reaction 12 plus. In March, 1932, entered infirmary with symptoms of acute respiratory infection and with a history of several recent mild "head colds," with persistent cough and lack of endurance. Râles heard in 2nd right interspace anteriorly. Roentgenogram revealed a definite parenchymatous lesion in lower part of right upper lobe, of exudative character. A subsequent tuberculin test was still very strongly positive.

In the total group of parenchymatous pulmonary lesions certain interesting facts stand out, more especially since the degree of allergy as manifested by the skin test was known before the appearance of clinical lesion. Definite lesion appeared at times within a period of 6 months following a negative roentgenogram. Three times it appeared as a fine, hard type of infiltration, the roentgen appearance of which may best be described by the word "scirrhous." These lesions were clearly proliferative in character and in none was the tuberculin reaction markedly positive either before the lesion appeared or at the time of its appearance. In none was the apex free. Two cases were unilateral, one bilateral. In all three, symptoms were practically negligible and any referable to the chest entirely lacking, the picture being one of a very mild toxic reaction.

In contrast to these productive (or proliferative) lesions were those of exudative character, which uniformly occurred in students with marked skin reactions. The earliest began as minute, poorly defined dots, usually not in the extreme apex. In a few months these dots had become faint but easily recognizable shadows, at times involving the apex but most marked in the 2nd and 3rd interspaces. The skin reaction remained markedly positive and clinically the patients presented symptoms suggestive of pulmonary disease.

It was interesting to note that not one of these early lesions betrayed the characteristics of the Assmann infraclavicular infiltration, which apparently has been rediscovered in recent years and possibly overemphasized. That the latter represents the "Modern Conception of Early Phthisis," as contended recently by Morlock (9), we cannot admit, although it cannot be denied that soft, bronchopneumonic, infraclavicular patches frequently initiate clinical tuberculosis in young people. They represent a *not uncommon* form, but *not* the sole form, of exudative lesion, although certainly one of the most striking.

From our own observations, then, it appears that two strikingly different reactions to tubercle bacilli may mark the onset of clinical pulmonary tuberculosis, based (as far as we could determine) at least in part upon the degree of allergy (as represented by the skin test) shortly before the development of the lesion. This much appears probable. The facts, however, may be interpreted in various ways and the temptation to speculate is strong.

Here, however, only the bare high-lights may be given.

DISCUSSION AND SUMMARY

1. Between 6 and 7 per cent of the student nurses in the University of California Hospital developed clinical tuberculosis during training. An additional 4 per cent have developed the disease since graduation.

2. The majority of nurses who failed to react to tuberculin on entrance also failed to react when rechecked.

3. Most of the nurses who developed clinical tuberculosis during training were positive reactors on entrance into training.

The natural outcome of such a study as the present one is the question, "What shall be done about tuberculous infection and disease among nurses?" Geer (*loc. cit.*) advises the adoption of the most rigid contagious technique where nurses come in contact with tuberculous patients. This is an excellent recommendation.

In the University of California Hospital, where the risk incident to the nursing of tuberculous disease is rarely encountered, emphasis has been placed upon repeated physical examinations and roentgenograms, checking of weight and an attempt to arouse what one might term a "tuberculosis consciousness" among the nurses and to enlist their cooperation in detecting and reporting symptoms and signs suggestive of tuberculous disease. At best this can only aid in the discovery of le-

sions at the earliest possible moment. We are far from a solution of the approach to control of tuberculosis in our students, but it is to be hoped that the increasing interest in the problem in various quarters will ultimately bring results.

In conclusion we wish to express our sincere thanks to Doctor Wm. J. Kerr for his unfailing interest and loyal support and to Doctor H. E. Ruggles and Doctor Robert Stone of the Department of Roentgenology for their coöperation and assistance. Suggestions of Doctor Allen K. Krause have been most helpful.

We gratefully acknowledge the aid of Doctor Hilda M. Davis and Doctor Evelyn M. Anderson and of the Nursing School Staff, in particular the supervisors of the Infirmary Unit, without which much of the detailed work would have been impossible.

REFERENCES

(1) WHITNEY, JESSAMINE S.: Tuberculosis among young women, Amer. J. Nursing, 1928, xxviii, 766.

(2) Decline in the death rate from tuberculosis; changes in age and sex distribution of the mortality in England and Wales during the last half century, Bull. N. Y. Tuberc. and Health Assn., 1927, vi, 4.

(3) MÜCKE: Die Tuberkulose des Pflegepersonels, Beitr. z. Klin. d. Tuberk., 1926, xiv, 155.

(4) HEIMBECK, J.: Tubercular immunity, Int. Clinics, December, 1927.

(5) SHIPMAN, S. J., AND DAVIS, ELIZABETH: Tuberculin hypersensitiveness and tuberculous disease among nurses, Amer. J. Nursing, 1928, xxviii, 769.

(6) GEER, E. K.: Tuberculosis among nurses, Arch. Int. Med., 1932, xlix, 77.

(7) VAN ZWALUWENBURG, J. G., AND GRABFIELD, G. P.: Apical pleuritis and its relationship in pulmonary tuberculosis, Amer. Rev. Tuberc., 1921, v, 323.

(8) BRITTON, J. A., AND BOLLMAN, E. B.: Tr. Nat. Assn. Study & Prev. Tuberc., 1925.

(9) MORLOCK, H. V.: The modern conception of early phthisis, Brit. Med. J., April 25, 1931, no. 3668, p. 702.

THE CORRELATION OF BLOOD COUNTS IN 150 CLINICAL CASES OF TUBERCULOSIS AND UNDERLYING PATHOLOGICAL CHANGES AS SHOWN BY SERIAL X-RAY FILMS[1]

JOHN W. FLINN, ROBERT S. FLINN AND ZEBUD M. FLINN

In the study of any infectious disease there are two very important objectives. The first is to ascertain the severity of the infection; the second to determine the powers of resistance of the host. Given these two factors, it is comparatively easy to calculate the condition of the patient and his prospects of recovery.

Thanks to the brilliant discoveries of Sabin and her coworkers, supplemented by those of Medlar and his associates, it is now possible to determine quite accurately these two factors in the disease tuberculosis. Sabin (1) says, "The specific reactions of the blood cells to tuberculosis are shown by two strains, monocytes and lymphocytes. In general, changes in the lesions are reflected by the monocytes; and in the resistance of the animal by the lymphocytes."

Medlar (2) says, "In the leucocytic reaction the mononuclear leucocyte represents new tubercule-formation. The neutrophile connotes tuberculous abscess-formation and the lymphocyte indicates healing of the tuberculous process." He adds that the mononuclear cells "also play a large part in the repair of caseated lesions."

These combined quotations represent our present *credo* regarding the leucocytic reaction of infection with the tubercle bacillus. This belief is based on the careful and extensive studies of these two groups of research workers, supplemented by rather careful clinical observations extending over a number of years.

Since the leucocytic response in tuberculosis is not specific, the blood-cell count "taken by itself cannot establish the diagnosis of tuberculosis" (3). It can, however, prove very suggestive, and, when considered in conjunction with a carefully taken history, well-established symptoms, definite physical and X-ray findings and with other laboratory reports,

[1] Read at a session of the Clinical Section at the twenty-eighth annual meeting of the National Tuberculosis Association, Colorado Springs, Colorado, June 5, 1932.

it often proves most useful in clinching a definite diagnosis of active tuberculosis.

It is after a definite differential diagnosis of tuberculosis is established that the leucocytic picture becomes of great value. It indicates quite accurately the underlying pathological processes in the affected organ at the time the blood count is made. It must not be forgotten, however, that the blood-cell count cannot give one a correct mental picture of the gross pathology of the affected organ. All it can do is to indicate the histopathological processes which are going on at the time the blood specimen is taken.

Serial blood-cell counts indicate quite accurately the progression of the pathological processes, but even they give very little information regarding the gross pathology.

In this connection it is well to remember that laboratory findings indicate pathological conditions, whether or not they are giving rise to clinical symptoms. Clinicians are becoming increasingly aware that pathological activity is the crucial test as to whether or not a tuberculous lesion is permanently healed. It is not enough to have the patient free from all signs of clinical activity. In addition to this, the clinician should convince himself that there is an entire absence of all pathological activity and that the lesion is so completely healed that it will not break down again under the ordinary stresses of life. It is in the solution of this most difficult problem that the blood-cell count presents one of the most practical phases of its usefulness.

As in former reports (4) (5), in the classification of cases we used the plan adopted by the National Tuberculosis Association as a basis. The first two divisions of this classification were adopted as outlined,—the minimal and the moderately advanced. From the third class, the far-advanced of the National Tuberculosis Association, a fourth class, "very far advanced—probably hopeless," was taken. This gave us four classes: (I) Minimal, (II) Moderately Advanced, (III) Far Advanced, and (IV) Very Far Advanced, probably hopeless.

Chart 1 shows the average number of monocytes, neutrophiles and lymphocytes per cubic millimetre in each of the four different classes in 1,325 consecutive cases of active pulmonary tuberculosis. It also records the average total white count in each class.

The average total white count, represented by the rising broken line at the top, begins at 7,220 in class I, rises to 8,051 in class II, to 9,089 in class III, and to 10,279 in class IV.

The average neutrophile percentage, represented by the upper mixed line, begins at 57.17 per cent in class I, rises to 59 per cent in class II, to 63.62 per cent in class III, and to 68.45 per cent in class IV.

The average monocyte percentage, represented by the rising dotted line, begins at 3.57 per cent in class I, rises to 3.85 per cent in class II, to 6.07 per cent in class III, and to 7.03 per cent in class IV.

The average lymphocyte percentage, represented by the falling solid line, begins at 37.18 per cent in class I, decreases to 36.3 per cent in class II, to 28.8 per cent in class III, and 22.74 per cent in class IV.

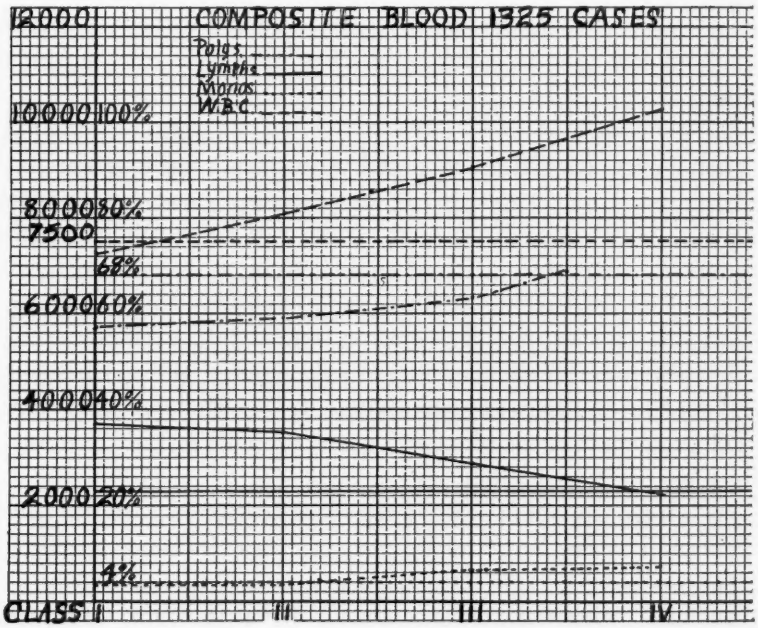


CHART 1

In a word, the total white count and the percentages of neutrophiles and of monocytes increase steadily as the disease progresses from the minimal to the very far-advanced stage. At the same time the percentage of lymphocytes decreases steadily. Our interpretation of these figures is that in class I there is very little extension of the tuberculous process taking place, either in the form of tubercle-formation (indicated by the number of monocytes in the circulating blood) or in the form of suppuration (indicated by the number of neutrophiles). As the disease progresses, both these processes (tubercle-formation and suppuration) extend and increase, as is manifested by an increase in the number of

monocytes and of neutrophiles in the blood-stream. Likewise, there is, as a rule, a large amount of healing going on in class I, as shown by the abnormally large number of lymphocytes in the circulating blood. As the disease progresses there is less and less tendency to heal, until in class IV the lymphocytes drop below the normal level, showing that little if any healing is taking place.

Chart 2 covers the same ground in the 150 consecutive clinical cases of tuberculosis comprising the present study. The results are so very

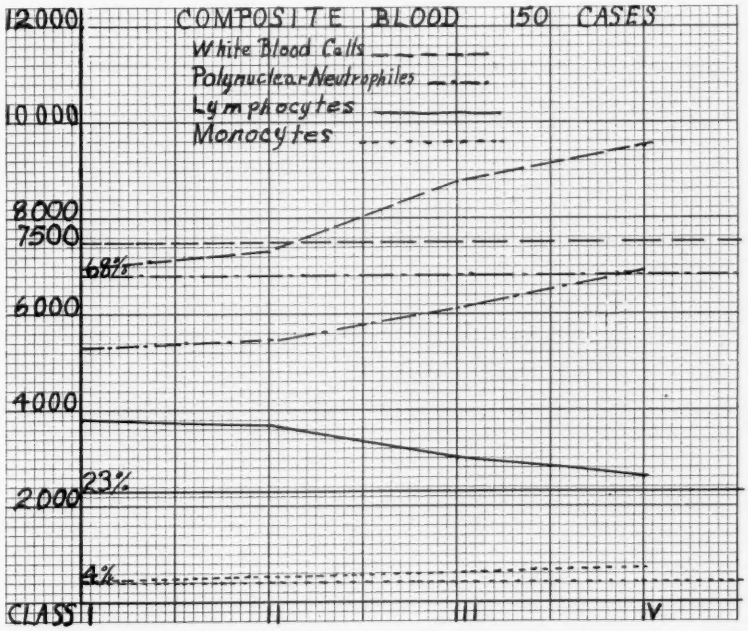


CHART 2

similar that we believe we are justified in drawing the same conclusions even from this much smaller number of cases.

The average total white count is appreciably lower throughout, varying from 6,978 in class I to 7,306 in class II, to 8,734 in class III, and to 9,543 in class IV. The rate of increase is appreciably less than in chart 1.

The neutrophile percentage is appreciably lower in the first three classes, but reaches a slightly higher level in class IV. It rises from 53.52 per cent in class I to 55.2 per cent in class II, to 60.50 per cent in class III, and to 68.67 per cent in class IV. This shows a considerably greater rate of increase than appears in chart 1.

The monocyte precentage is very considerably higher in class I and

class II and practically the same in class III and class IV. This makes the total rate of increase considerably less than in chart 1. This percentage varies from 4.91 in class I to 5.48 in class II, to 6.0 in class III, and to 7.04 in class IV.

Taken as a whole, this smaller number of cases seems to us to show less suppuration in the first three classes, more tubercle-formation in the first two classes, and more healing in all classes than is shown in the larger number of cases represented in chart 1. The total figures however seem to us to corroborate the conclusions drawn from chart 1.

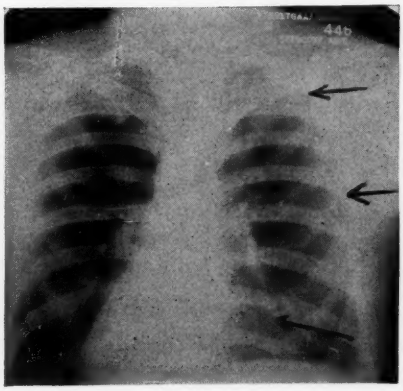


FIG. 1

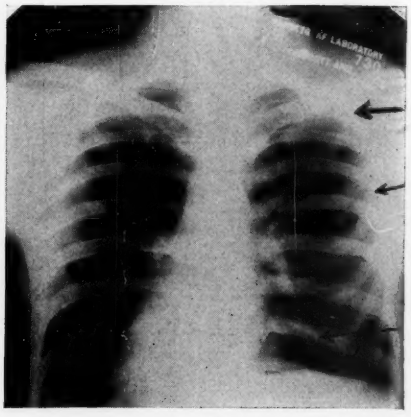


FIG. 2

Case 1: Class I: Minimal

Stereo X-ray films no. 446 (figure 1), exposed March 31, 1931, show: *Left lung:* Linear markings increased. A few reach the surface, to end in small discrete areas of slightly increased density. Old pleurisy over base. *Right lung:* Generalized increase of linear markings. A number can be traced to the surface, especially in the apex and axilla, to end in small areas of increased density. These areas mostly appear discrete and clear-cut, but a few have somewhat indefinite edges. The inner quarter of the base shows a number of fuzzy areas of increased density.

Blood: Haemoglobin 89 per cent; r.b.c. 4,540,000; w.b.c. 5,500; polys. 56.0 per cent; lymphocytes 38.0 per cent; monocytes 2.5 per cent.

Sputum negative; urine normal; Wassermann negative. Erythrocyte sedimentation rate 9 hours. O. T. skin test positive, plus.

Stereo X-ray films no. 730 (figure 2), exposed March 7, 1932, about a year later show: *Left lung:* Linear markings are increased. A few reach the sur-

face to end in small discrete areas. *Right lung:* Linear markings are increased. Many reach the surface in the upper part of the lung, to end in small discrete areas. Small discrete areas of increased density over inner quarter of base.

Blood: (January 7, 1932): Haemoglobin 102 per cent; r.b.c. 5,200,000; w.b.c. 5,800; polys. 56.0 per cent; lymphocytes 38.5 per cent; monocytes 4.5 per cent.

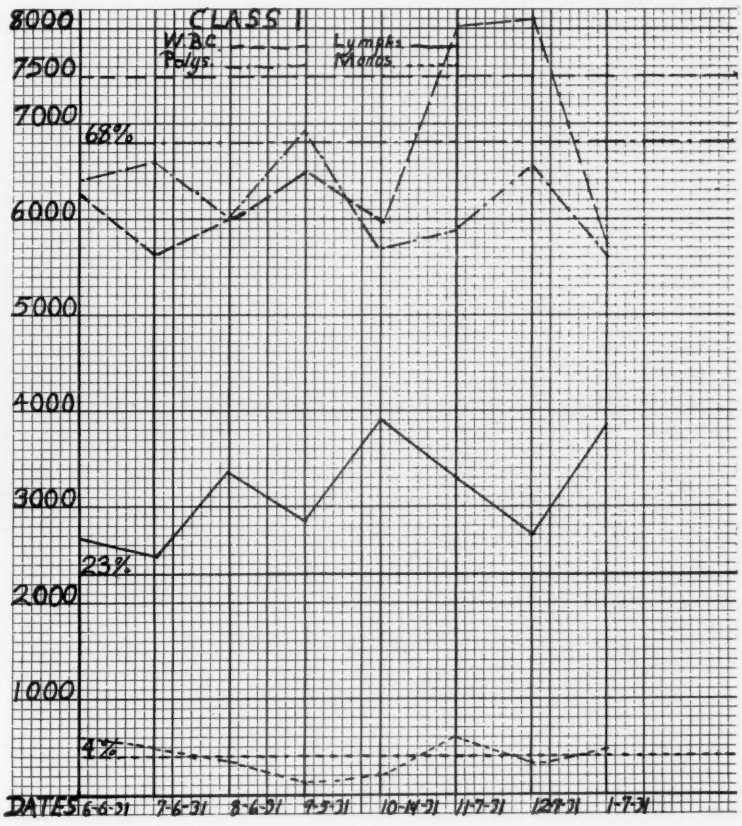


CHART 3

The red part of the blood-picture has improved noticeably in the intervening ten months. The total white count remains almost exactly the same as do also the percentage of neutrophiles and of lymphocytes. The only noticeable change is in the percentage of monocytes, which suggests that there is some "clearing" taking place in connection with the large amount of healing (lymphocytes 38 per cent), which has been going on steadily.

Chart 3 shows a series of eight consecutive monthly blood-cell counts

on this case (case 1, class I) from June, 1931, to January, 1932, inclusive. The total white count and the percentage of neutrophiles both remain low, except in November and December, when they both show a noticeable rise, at the time of an acute upper respiratory-tract infection.

The percentage of lymphocytes shows a steady and satisfactory increase except at the time of the acute infection, when it decreases quite rapidly. The percentage of monocytes decreases for the first four months, rises at the time of the acute infection, and remains around a high normal during the remaining period of observation.

Case 2: Class II: Moderately Advanced

Stereo X-ray films no. 372 (figure 3), exposed October 3, 1930, show: *Left lung:* Infiltration with fuzzy edges, apex to upper border of 7th rib and 10th v.s. Area suspicious of cavitation beneath the clavicle. *Right lung:* Infiltration from apex to 1st interspace with fuzzy edges.

Blood: Haemoglobin 90 per cent; r.b.c. 4,610,000; w.b.c. 6,050; polys. 67.0 per cent; lymphocytes 26.5 per cent; monocytes 5 per cent.

Sputum positive; urine normal; Wassermann negative. Erythrocyte sedimentation rate 1½ hours. O.T. skin test positive, plus.

Stereo X-ray films no. 468 (figure 4), exposed April 28, 1931, about seven months later, show: *Left lung:* Generalized increase of linear markings. Many reach the surface of upper part of lung. Scattered throughout the upper two-thirds of the lung field are small areas of slightly increased density which appear discrete. *Right lung:* Linear markings are increased. Many reach the surface to end in small discrete areas. Discrete infiltration from apex to 1st interspace and 6th v.s.

Blood: Haemoglobin 100 per cent; r.b.c. 5,080,000; w.b.c. 6,150; polys. 40.1 per cent; lymphocytes 51.0 per cent; monocytes 7.0 per cent.

The red part of the blood-picture has improved noticeably in the seven months. The total white count remains practically the same although there has been a marked decrease in the percentage of neutrophiles (67 to 40.1 per cent) and an even more marked increase in the percentage of lymphocytes (26.5 to 51 per cent). The consistently high monocyte percentage with an accompanying very high lymphocyte percentage during this period of pulmonary improvement suggests that the monocytes were acting as scavengers, and so assisting the lymphocytes in the healing process.

Chart 4 shows a series of 13 consecutive monthly blood cell counts on this case (case 2, class II) from September 30, 1930, to September 28,

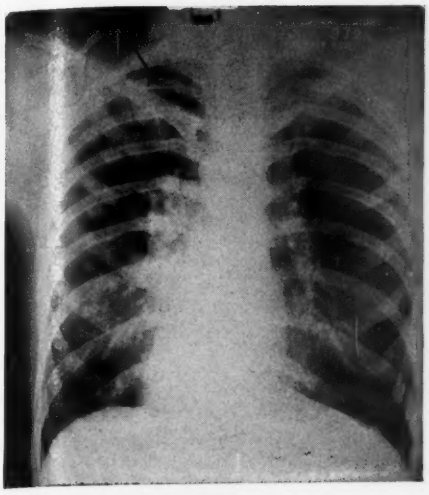


FIG. 3

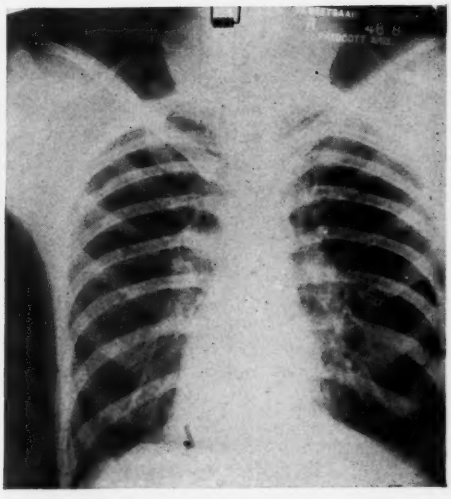


FIG. 4

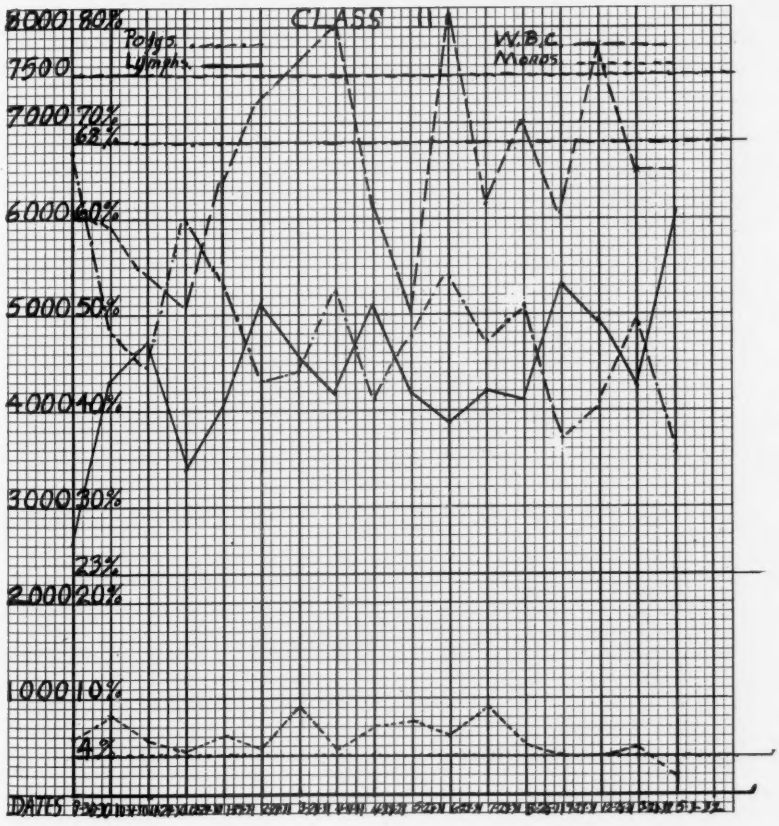


CHART 4

1931. It also shows an extra count made on April 4, 1931, and 3 subsequent blood counts, three, six and seven months later. The total white count for the greater part of the time remained well below the normal line. The three times when it went above the normal line there was a corresponding increase in the percentage of lymphocytes, showing that the latter were mainly responsible for the total increase. The neutrophiles decreased rather consistently. The most noticeable feature is the consistent and marked rise in the percentage of lymphocytes, indicating, as we believe, a great and increasing amount of healing. The monocytes were high for the first twelve months. This high percentage of monocytes, when accompanied by a high percentage of lymphocytes, indicates, we believe, that the monocytes were acting as scavengers, and were responsible for the large amount of "clearing" which the X-ray films showed had taken place in both lung fields.

Case 3: Class III: Far Advanced

Stereo X-ray films no. 130 (figure 5), exposed November 16, 1929, show: *Left lung:* Infiltration from apex to 3rd rib and 7th v.s. There is a large cavity, measuring 6 x 3 cm., reaching from the 1st to 3rd ribs and from the 3rd to 5th v.s. interspaces. It has a fairly heavy wall of collateral inflammatory reaction around it. *Right lung:* Infiltration from apex to 2nd rib and 7th v.s. It is moderately dense, and contains two areas of apparently decreased density beneath the 2nd rib. They measure 2 x 2.5 cm. and 1 cm. in diameter.

Blood: Haemoglobin 95 per cent; r.b.c. 4,530,000; w.b.c. 10,800; polys. 71.5 per cent; lymphocytes 24.0 per cent; monocytes 4.0 per cent.

Sputum positive; Wassermann negative; urine normal.

Stereo X-ray films no. 528 (figure 6), exposed July 16, 1931, about twenty months later, show: *Left lung:* Increase of lower main-stem bronchus. Generalized increase of linear markings: a number reach the surface to end in small discrete areas. Sparse infiltration from apex to 2nd rib and 6th v.s. It is made up of small discrete areas of increased density. *Right lung:* Infiltration from apex to 2nd interspace and 7th v.s. It is made up of areas varying in size and density which mostly appear clear-cut and hard. Beneath the clavicle and 2nd rib is an area, measuring 2 cm. in diameter, of apparently decreased density. Scattered throughout the lower lobe are small areas of discrete increased density.

Blood: Haemoglobin 91 per cent; r.b.c. 4,840,000; w.b.c. 8,000; polys. 55.0 per cent; lymphocytes 35.5 per cent; monocytes 6.5 per cent.

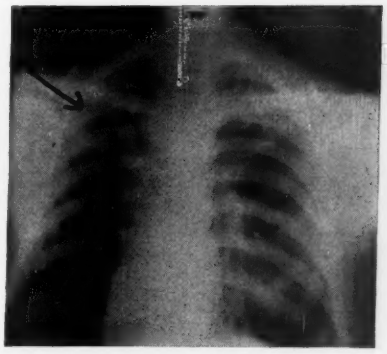


FIG. 5

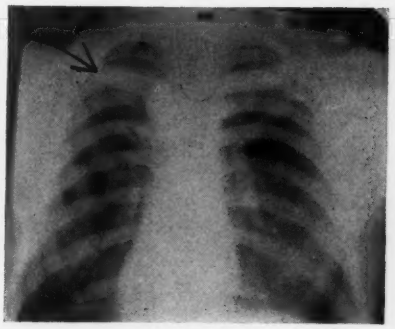


FIG. 6

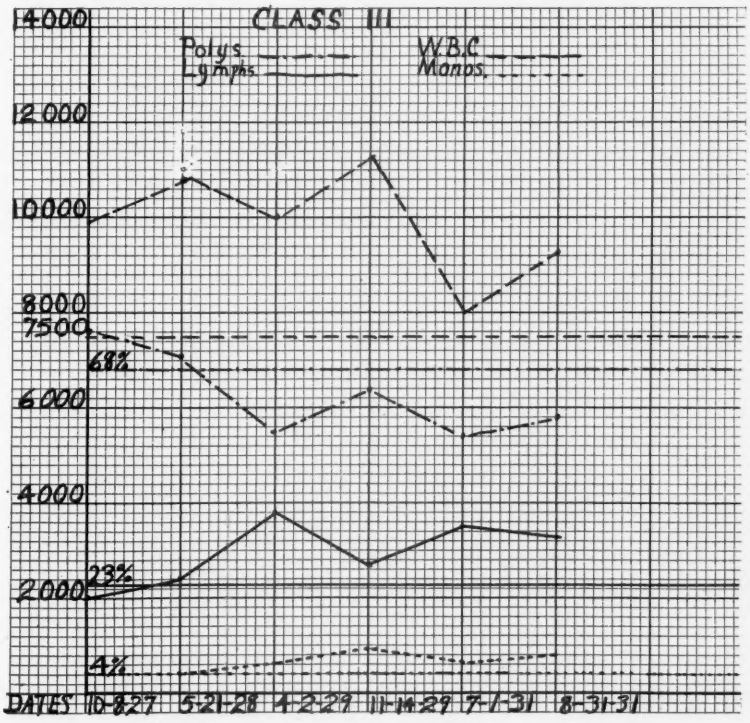


CHART 5

During these twenty months there has been rather remarkable improvement in the pulmonary condition, with complete closure of the large cavity in the upper left. In the same period the red part of the blood-

picture remained practically the same, but there has been a very noticeable change in the white part of the picture. There has been a distinct decrease in the total number of white cells, with a very noticeable decrease in the percentage of neutrophiles and a corresponding increase in the percentage of lymphocytes. The increase in the monocytes, in conjunction with a high lymphocyte percentage, we again associate with the "clearing" process in the lungs.

Chart 5 shows a series of six blood-cell counts on this case (case 3, class III), taken at irregular intervals over a period of nearly four years. The total white count for the first two years remained quite high, but decreased very considerably during the last two years. The neutrophiles decreased very considerably, with a corresponding increase in the lymphocytes. The high monocyte percentage, when accompanied by the high lymphocyte percentage, we again associate with the "clearing" in the lung fields.

Case 4: Class IV: Very Far Advanced, Probably Hopeless

Stereo X-ray films no. 583 (figure 7), exposed September 5, 1931, show diffuse fine fuzzy infiltration from apex to base in both lungs. Probable cavitation in right upper. Physical examination confirmed the above findings and we at that time made the following note: "Our conception of this case is that ulceration took place into a branch of the pulmonary artery in the cavity in the right upper lobe, resulting in the formation of miliary tubercles in the interstitial tissues in both lungs. For some time, we would presume, this miliary condition would be manifest only by X-ray films, as no physical signs would exist. Later, we take it, the condition became complicated with a perifocal exudative process of toxic origin which gave rise to physical signs."

Blood: Haemoglobin 80 per cent; r.b.c. 3,340,000; w.b.c. 8,600; polys. 72.5 per cent; lymphocytes 22.5 per cent; monocytes 5 per cent.

No sputum; Wassermann negative; urine normal. Erythrocyte sedimentation rate, 45 minutes.

Stereo X-ray films no. 733 (figure 8), exposed March 25, 1932, after six months of intensive bed-pan rest, show: *Left lung:* Increase of linear markings. A few reach the surface. Indefinite areas of slightly increased density throughout the entire lung field. These areas are moderately dense above the 1st rib. *Right lung:* Generalized increase of linear markings. Many reach the surface. Small indefinite areas of slightly increased density are scattered throughout the lung fields. They are slightly more dense above the 1st rib.

Blood: Haemoglobin 95 per cent; r.b.c. 5,100,000; w.b.c. 6,450; polys. 42.5 per cent; lymphocytes, 47.6 per cent; monocytes, 6.0 per cent.

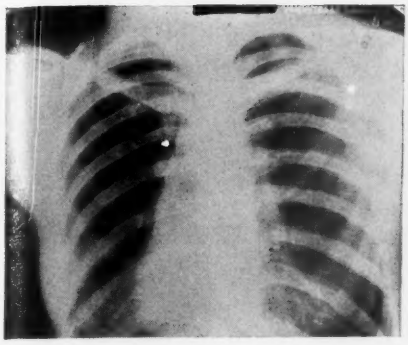


FIG. 7

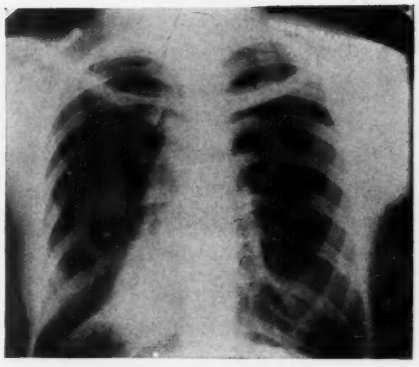


FIG. 8

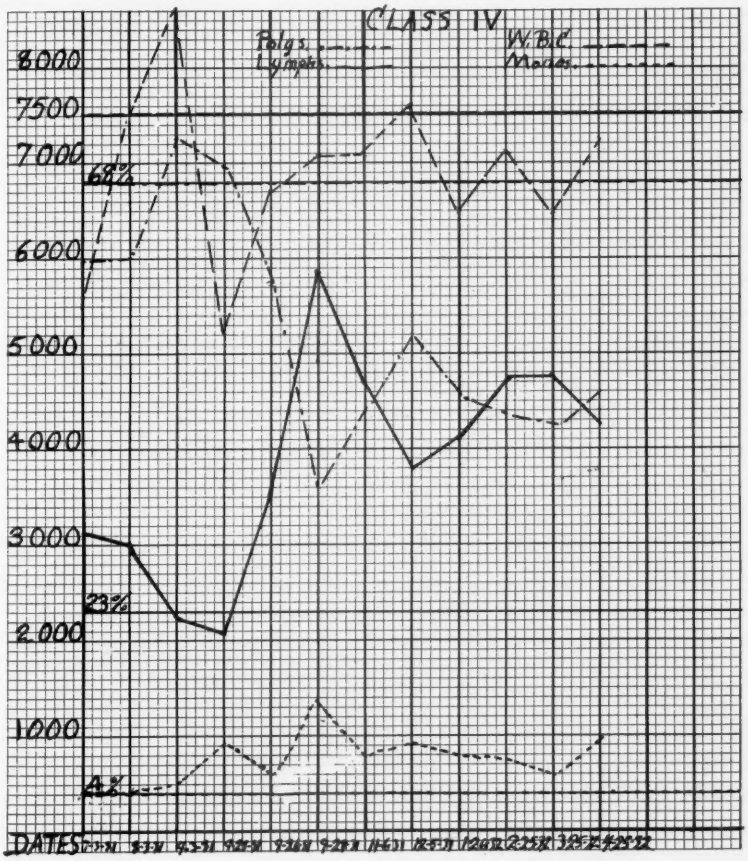


CHART 6

There has been a marked improvement in the red part of the blood-picture in the intervening six months. The total white count has decreased noticeably and the percentage of neutrophiles has decreased very markedly. The percentage of lymphocytes has more than doubled. The percentage of monocytes has remained high, suggesting a large amount of "clearing." Study of the X-ray films in this case showed a very unusual amount of clearing in both lung fields.

Chart 6 shows a series of 10 consecutive monthly blood-cell counts on this case (case 4, class IV) from July, 1931, to April, 1932, inclusive. It also shows two extra counts made in September.

This is a very interesting graph. It indicates that this patient had an acute exacerbation of the disease soon after coming under observation, in which the total whites, the neutrophiles and the monocytes all increased rapidly, with a corresponding decrease in the lymphocytes. Then she suddenly began to improve, as indicated by a sharp drop in the neutrophiles and the monocytes, with a corresponding rise in the lymphocytes. She then improved steadily, with the neutrophiles low, the lymphocytes high and the monocytes following the lymphocytes fairly closely.

These changes were indicated just as distinctly in the stereo X-ray films. The films exposed August 8, 1931 showed "an increase in the size and in the density of the areas of increased density throughout both lungs. There has also been an increase in the numbers of areas of increased density. . . . .No evidence of any clearing or hardening. The edges of the areas just as fuzzy as on July 6, 1931."

The films exposed September 22, 1931 showed: "*Left lung:* A definite increase in the number of fuzzy areas of increased density. *Right lung:* A considerable and definite increase in the number of fuzzy areas of increased density." Films exposed November 2, 1931 showed: "*Left lung:* A great amount of definite clearing throughout. A slight amount of hardening. *Right lung:* A great amount of definite clearing throughout. Definite hardening throughout."

When we consider this graph in connection with this patient's spectacular lung improvement, as shown by X-ray, it represents a tremendously interesting and suggestive series of blood-pictures.

We offer a word of apology for seeming to suggest that this is a typical class-IV case. While the case certainly belonged in class IV on entering, it is very far from typical of this class in the results obtained from treatment. The very spectacular results, reflected equally well in the serial blood-cell counts and in the serial X-ray films, is our excuse for presenting it in this study.

Case 5: Class III: Phrenic Neurectomy

Stereo X-ray films no. 134 (figure 9), exposed December 8, 1929, show: *Left lung:* Thickened pleura over apex. There is an area of increased density, reaching from the apex to the 2nd rib and 7th v.s. In the 2nd interspace is an area of apparent decreased density, measuring 1.5 cm. in diameter. Reaching from the 1st to the 2nd rib is a well-defined cavity, measuring 4 x 3 cm. *Right lung:* Increase of hilum shadow, lower main-stem bronchus and linear markings. Many of the linear markings reach the surface to end in small discrete areas.

Blood: Haemoglobin 88 per cent; r.b.c. 4,860,000; w.b.c. 8,650; polys. 50 per cent; lymphocytes 35 per cent; monocytes 12 per cent.

Sputum positive; Wassermann negative; skin test positive, plus, plus; urine, albumin, hyaline casts, pus-cells.

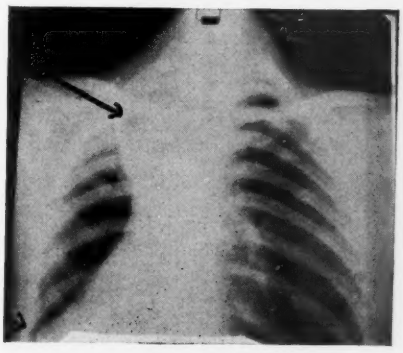


FIG. 9

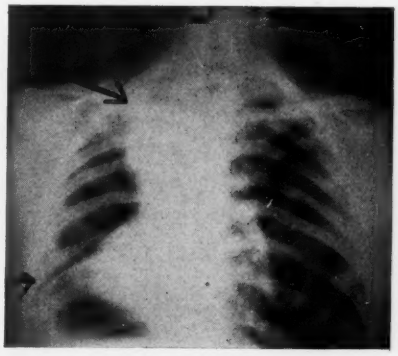


FIG. 10

This case had responded well to many months of fairly complete bed-rest, during which the right lung and lower left lung had cleared up satisfactorily. The cavitation in the upper left, however, failed to close. The blood-picture was quite satisfactory, except for the percentage of monocytes, which remained very unusually high. Although the lymphocyte percentage was high, we did not feel justified in attributing 12 per cent monocytes to a scavenging process. Our previous experiences had led us to associate so high a monocyte percentage with extensive tubercle-formation,—probably extrapulmonary. Taking this in conjunction with the urinary findings led us to strongly suspect a genitourinary tuberculosis.

After a week's intensive study of the case, a very competent urologist was not able to detect any pathological process in the genitourinary tract. We therefore did a left phrenic neurectomy in December, 1929.

Stereo X-ray films no. 273 (figure 10), exposed July 1, 1931, about a year and a half later, showed: *Left lung:* Homogeneous increased density from apex to 2nd rib and 6th v.s. Below this throughout the lung field are scattered small areas of discrete increased density. *Right lung:* Increase of hilum shadow, lower main-stem bronchus and linear markings. Many linear markings reach the surface to end in small discrete areas of increased density.

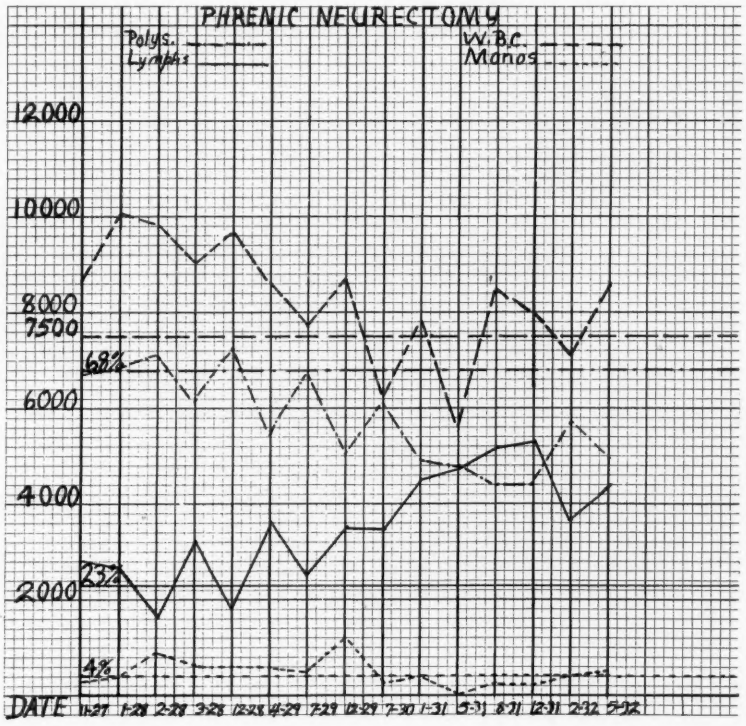


CHART 7

Blood: Haemoglobin 95 per cent; r.b.c. 5,120,000; w.b.c. 8,250; polys. 38.0 per cent; lymphocytes 57.0 per cent; monocytes 4.0 per cent.

Urine normal.

During the intervening nineteen months the cavitation in the upper left lung closed completely. The red part of the blood-picture improved noticeably. The total white count remained about the same, but the percentage of neutrophiles decreased greatly, and there was a corresponding increase in the percentage of lymphocytes. The monocytes decreased to normal. The urine became normal.

We therefore concluded that the unusually high percentage of monocytes in December, 1929, had probably indicated quite extensive tubercle-formation in and around the wall of the cavity in the upper left lung. The toxic absorption from this area probably accounted for the urinary findings.

Chart 7 represents a series of 15 blood-cell counts on this case (case 5, class III, phrenic neurectomy), taken at irregular intervals over a period of about four and one-half years. During the first three months the total white count, the neutrophile percentage and the monocyte percentage all increased noticeably, with an even greater decrease in the percentage of lymphocytes, suggesting an acute spread of the disease.

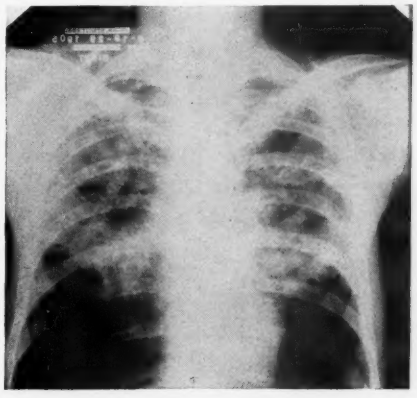


FIG. 11

After the third month there was a quite steady and consistent improvement in all parts of the white picture. The total white count, the percentage of neutrophiles and of monocytes all decreased satisfactorily, with a rather marked increase in the percentage of lymphocytes. The only marked exception to this was in the marked increase of monocytes in the latter part of 1929, which disappeared after the phrenic neurectomy.

Case 6: Class IV: Very Far Advanced, Probably Hopeless

Stereo X-ray films (figure 11), exposed September 4, 1929, show extensive fibrocaseous infiltration throughout all of the right and left upper lobes. Numerous areas of ulceration scattered throughout both lungs. Considerable fibrosis. Pleura markedly thickened over both bases. Pleural diaphragmatic adhesions to both domes of the diaphragm.

Blood: Haemoglobin 63 per cent; r.b.c. 3,780,000; w.b.c. 9,850; polys. 79.5 per cent; lymphocytes 10.0 per cent; monocytes 10.5 per cent.

Sputum positive; Wassermann negative; urine, albumin and casts.

This patient died within a month. The case is reported here as being much more nearly typical of class IV than case 4 previously described.

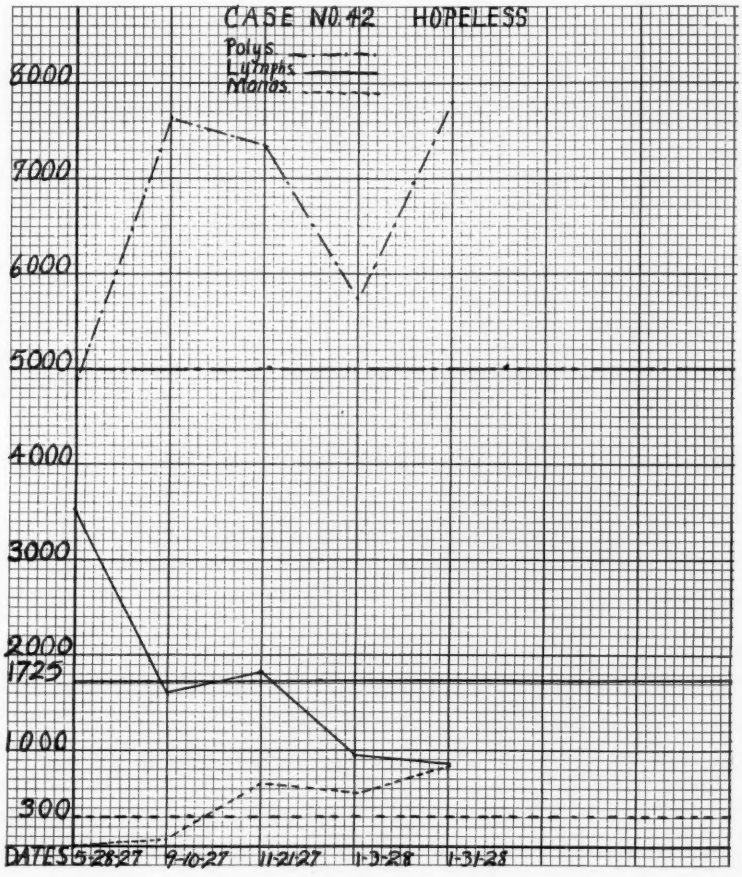


CHART 8

There is marked anaemia. The total white count, the percentage of neutrophiles and the percentage of monocytes are all greatly increased, with a corresponding decrease in the percentage of lymphocytes. The monocyte-lymphocyte ratio is one.

Chart 8 (previously published) represents a series of blood-cell counts

on a very far-advanced case of pulmonary tuberculosis taken at irregular intervals over a period of eight months. During the first three and one-half months, there was a rapid rise in the neutrophiles, with a corresponding fall in the lymphocytes. The monocytes remained very low. During the next two months the neutrophiles and the lymphocytes remained about stationary, while the monocytes increased rapidly.

During the last two months the lymphocytes decreased rapidly, until this line practically met that of the monocytes, which had still further increased. The neutrophiles, after a sharp drop, increased rapidly toward the end. This chart is shown to further emphasize the changes in the blood-cell count in terminal cases of pulmonary tuberculosis.

CONCLUSIONS

This short study serves to confirm the conclusions, hypotheses and impressions stated by two of us in a former article (5).

Considering the results of this study in greater detail and along the lines suggested in the title of this symposium, we find that the blood-cell count is of very minor importance in the differential diagnosis of tuberculosis. At the best it can be only suggestive.

When a diagnosis of tuberculosis has been definitely established, the blood-cell count becomes of great importance. Not only does it aid greatly in differentiating between a pathologically active and a healed lesion, but it also indicates quite accurately the type of pathological activity which is present and how this type changes from time to time.

We are still obsessed with the idea that the widest sphere of usefulness of the blood-cell count in clinical tuberculosis is in prognosis and treatment. It enables the clinician to determine the severity of the infection by the monocyte and the neutrophile counts and the powers of resistance of the body tissues by the lymphocyte and the monocyte counts. Later it assists him very materially in ascertaining when pathological activity has completely ceased. Thus he is enabled to give his patient a fairly correct prognosis at any stage of the disease, and to determine quite accurately how intensive a treatment should be adopted and how long it should be continued.

DISCUSSION

John W. Flinn (in closing)

Replying to the two speakers who expressed the opinion that the blood-cell count is not of prognostic value in tuberculosis:

This question may be considered from the standpoint of the pathologist and from that of the clinician. Viewing the question pathologically, we will quote from the official abstracts, prepared by the two distinguished pathologists, of the most interesting papers presented by them before this joint session this afternoon.

Dr. Sabin described two phases in tuberculous infection in animals. In the first phase "Changes in the blood-cells reflect faithfully changes in the lesions." In the second phase "The blood cells reflect more directly variations in resistance on the part of the animal."

Dr. Medlar refers to two types of lesions in human tuberculosis. The first type "is a lesion representative of a successful resistance of the host against a virulent infection and hence is retrogressive in character." It consists of "tubercle with a small area of caseation, with giant cells, with increased reticulum and with lymphocytic infiltration." The second type is "The progressive spreading lesions . . . . in which the virulent bacilli are in the ascendency. In these lesions the neutrophile plays the chief rôle." Dr. Medlar adds, "Since the various leucocytes are present in the general circulation prior to their participation in inflammatory lesions, it seems but logical that the circulating leucocytes would give information relative to the type and severity of the pathological process."

Does it seem logical to deny that such information as these two authorities state can be got from blood-cell counts regarding "changes in the lesions," "variations in resistance on the part of the animal" and "the type and severity of the pathological process" is not of prognostic value in tuberculosis?

In a quite recent article (April, 1931) Medlar and his associate state that "The following quotations are in accord with our own observations: 'The serial prosecution of haemogram forms or curves . . . . permits us to establish the PROGNOSIS better than any other method of investigation'" (6).

Considering the question clinically, we have presented carefully obtained laboratory findings in 1,325 consecutive cases of clinical tuberculosis and have drawn our conclusions from these. We have also presented a more detailed study of a group of 150 consecutive cases, which has served to confirm these conclusions. When those who hold a contrary opinion present a similar amount of clinical evidence in support of that opinion, we will gladly begin to reconsider and, if possible, to revise our conclusions.

The most interesting and instructive paper of Dr. David Smith showed conclusively that we clinicians did not begin to really appreciate the value of the blood-cell count in the study of our cases of tuberculosis until the pathologists had taught us the true significance of these findings.

REFERENCES

(1) SABIN, F. R.: Amer. Rev. Tuberc., 1932, xxv, 157.
(2) MEDLAR, E. M.: Ibid., 1929, xx, 339.
(3) MEDLAR, E. M., AND KASTLIN, G. J.: Ibid., 1927, xvi, 706.
(4) FLINN, J. W.: Ann. Int. Med., January, 1929.
(5) FLINN, J. W., AND FLINN, R. S.: Amer. Rev. Tuberc., 1929, xx, 347.
(6) MEDLAR, E. M., AND PESQUERA, G. S.: Ibid., 1931, xxiii, 389.

THE USE OF FILTERED-AIR CHAMBERS IN PULMONARY TUBERCULOSIS[1]

ALVAN L. BARACH

Storm van Leeuwen (1) first suggested the use of so-called allergen-free chambers for the treatment of asthma in 1924. These chambers consisted of rooms lined by an asbestos material (eternite) to prevent the growth of microörganisms. The ventilation was accomplished by blowing air from a height of about 35 metres above the soil through metal pipes into the chamber. The air was heated before it entered the chamber. In some cases the outside air was blown over a cooling medium, and, in the process of condensation, was partially deprived of the dust in the air. Of 500 patients with asthma treated in his clinic 75 per cent were completely or almost completely cured in some days, about 50 per cent materially improved in some weeks, and 10 per cent remained unaltered. The favorable results observed were ascribed by him to the removal of microörganisms, prevailing in the air, which were considered allergic and therefore toxic to the patient with asthma. Since then filtered-air chambers have been used in the treatment of asthma by Leopold and Leopold (2), Cohen (3), Rappaport, Nelson and Walker (4) and others. Cases of pollen- and dust-asthma were generally, according to these reports, decidedly benefited by residence in chambers, in which most of the dust contained in the air was removed, although the results observed in America have not been as brilliant as those described by van Leeuwen. In our own chamber two cases of dust-asthma have been observed in which definite relief took place during the period of residence in the filtered-air chamber.

Van Leeuwen (5) subsequently noticed

that some patients with asthma combined with tuberculosis did extremely well. They were relieved not only of their asthmatic attacks but also of their pulmonary tuberculosis in a relatively short time. These cases, although not large in number, were the more impressive since the patients had been treated before in sanatoria with little success in low altitude.

[1] From the Department of Medicine, Columbia University, and the Presbyterian Hospital, New York City.

The improvement in the tuberculous patient was ascribed to the lack of climatic allergens in the air and was compared to the beneficial influence which air at high altitude exerts. A series of uncomplicated tuberculous subjects was then reported, most of whom appeared to show definite improvement as a result of the removal of allergens, that is, microörganisms, from the air.

In the allergen-proof chambers employed, only a part of the dust and bacteria in the air could be removed. No actual dust counts were made (6). It seemed desirable to the author to construct a chamber in which a maximal filtering of dust and bacteria from the air was accomplished, in order to test the hypothesis that arrest of active pulmonary tuberculosis could be specifically related to the removal of so-called allergic bacteria in the air.

An aluminum-walled, leak-tight oxygen room, having a cubic area of 1300 cu. ft., was employed. A motor-driven fan delivered 1300 cu. ft. of fresh air per minute through a finely woven wool-filter (Staynew) into the chamber, where it was passed over 1,000 linear feet of cold one-inch pipe containing brine. The air thus chilled and deprived of the greater part of its moisture through condensation on the cold pipes was heated to the desired temperature by a steam radiator on the opposite side of the room and then returned by ducts, 12 inches square, to the fan. The air was derived from a height of eight stories above the soil. The temperature was maintained between 64° and 68°F., and the humidity between 35 and 40 per cent. The entire volume of room-air was thus filtered every minute.

The most satisfactory method for determining the number of particles of dust in the air appeared to us to be the Jet or Konimeter (7) type of apparatus. The Owens Jet (8) apparatus was employed in this investigation. The instrument consists of a pump which draws measured quantities of air through a narrow orifice to a glass surface. The dust adheres to the glass and is later examined microscopically. The calculation of the number of particles per cubic centimetre is made by counting the particles seen under high power in a portion of the dust area. The actual count is then related to the volume of air withdrawn and magnification employed, thus:

$\frac{N \times S}{V}$ equals number of particles per cubic centimetre

N equals number of particles in each section of area

S equals number of sections in total area
V equals volume in cubic centimetres of total sample of air

The various weight methods of determining the dust content of the air did not seem applicable to the present study, since different particles of dust have different sizes and weights and our interest was primarily directed toward the quantitative measurement of the reduction in the *number* of dust particles in a filtered-air room.

Air taken directly from the filter consistently shows less than one per cent of the number of dust particles in the ordinary room-air. When 6,000 cu. ft. of air is passed over petri dishes, subsequent culture shows either no organisms or at most one colony. The air in the chamber itself, with a patient inside, contains a larger number of dust particles and bacteria due to the movement of the bed clothes and linen as well as the movement of patient or nurse in the room. The character of the dust particles, however, in a room which has been filtered shows a larger proportion of cotton and wool derived from clothes and bed linen. The average of ten dust-counts in the chamber and outside the chamber are as follows:

Chamber: 135 particles per cubic centimetre
Laboratory: 418 particles per cubic centimetre
Out-patient clinic: 501 particles per cubic centimetre

Inasmuch as many of the particles counted in the chamber are derived from the clothing and linen surrounding the patient, the actual filtration of allergic substances in the air is greater than the figures indicate. This is borne out by the following data on the number of microörganisms inside and outside the chamber.

Bacterial counts were made by exposing petri dishes for a constant time interval in various parts of the hospital. It should be noted that the hospital is in a district far up-town, near the Hudson river, and relatively free from the dust of a crowded community. The following results were obtained, exposing petri dishes for 45 minutes:

Chamber (with patient inside): 12 colonies per plate
Ward: 58 colonies per plate
Laboratory: 58 colonies per plate
Out-patient clinic: 88 colonies per plate

The air in the chamber thus contains from 14 to 20 per cent of the number of bacteria present in the ward, laboratory or out-patient clinic of the

hospital. The number of dust particles in the chamber is 27 per cent of that found in the out-patient clinic.

The inhalation of dust containing large amounts of silica produces a diffuse fibrosis in the lung and increases the susceptibility to tuberculous infection (9). Small amounts of silica present in ordinary dust derived from pavements and roads are without such influence as far as is known. Although this type of dust would be removed by the filter, it is doubtful that a favorable effect would be derived from the absence of such small quantities of silica. Whether air-borne bacteria have allergic properties that maintain tuberculous infection of the lungs is the particular problem which we have investigated by the use of a chamber in which, as far as possible, both the actual dust content and the bacterial content of the air has been diminished.

Results: The case histories of three patients follow:

Case 1: Male, Porto-Rican, age 24. *Family history:* Mother died of tuberculosis. *Present illness:* Three months before admission patient developed a chronic productive cough and began to lose weight. Three weeks before admission he had a severe haemoptysis of from 1 to 2 pints of blood followed by heavy streaking of the sputum, frequent pains in his chest and night-sweats. He lost 15 pounds during this period. *Physical examination:* Showed a well-nourished and developed Porto-Rican, male adult. *Lungs:* Dulness, broncho-vesicular breathing, and medium course râles above 3rd right interspace anteriorly and 6th vertebral spine posteriorly, with increased whispered voice. On left side, a few dry clicks above 3rd left interspace were heard. Temperature 98.4 to 100°, pulse 66 to 102, respirations 18 to 22. Sputum positive for tubercle bacilli, urine negative, weight 119 pounds. Stereo X-ray of chest showed a fibrocaseous infiltration, involving both upper lung fields, most marked on the right. On the left side only the apex was involved, whereas on the right the lung field appeared involved in both apex and 1st interspace. There were two large thick-walled cavities on the right side and a smaller one on the left underneath the first rib.

Diagnosis: Bilateral pulmonary tuberculosis.

Course: The patient ran an essentially stationary course during a period of 11 weeks in the filtered-air chamber. The temperature range during the last week was between 98° and 100°, pulse 68 to 88, respirations 20 to 22. The lung signs were unchanged. The patient gained four pounds in weight. The X-rays showed no change until six weeks after entrance to the chamber, when a definite spread of the infiltrated processs on the right side occupying practically the entire two-thirds of the 2nd interspace was observed. There was some increase in the circumfocal reaction about the cavity, which appeared to be smaller than on a previous film.

Case 2: Male, Porto-Rican, age 23. *Present illness:* Patient gave a history of pulmonary tuberculosis of approximately 1½ years' duration. After a period of four months' treatment at the Metropolitan Hospital he was discharged and resumed work, eight months ago. After two weeks, productive cough, chest pains, fever and night-sweats returned. He gradually lost 7 lbs. in weight, and finally entered Bellevue Hospital, whence he was transferred to the Presbyterian Hospital after ten days. He lost 7 lbs. during the past eight months. Six months ago he had a left phrenicectomy. *Physical examination:* Showed an apparently well-developed and well-nourished adult male. *Lungs:* Harsh, bronchovesicular breathing and medium and coarse râles on the left side above the 3rd interspace anteriorly to the 5th vertebral spine posteriorly. Temperature 97.4° to 100.6°, pulse 74 to 112, respirations 20 to 22, sputum positive for tubercle bacilli, urine showed faint trace of albumin with occasional hyaline and granular casts, weight 133½ pounds. Stereo X-ray of the chest showed an extensive infiltration in the left apex and 1st and 2nd interspaces, indicating fibrocaseous tuberculosis. Three cavities were present in the left 1st interspace. There was a soft flocculent infiltration in the right 1st and 2nd interspaces. There was some peribronchial infiltration in the lower left lobe.

Course: The patient ran an essentially stationary course during the 11 weeks in the filtered-air chamber. The temperature range during the last week was 98° to 99.6°, pulse 68 to 92, respirations 20 to 22. He gained 2 lbs. in weight. Sputum continued positive; lung signs were essentially unchanged: X-ray showed little definite change except for slight increase in the infiltration along the ramifications of the bronchi on the left side and probably a slight increase in the mottling in the outer halves of the first and second interspaces on the right.

Case 3: American, male, age 29. *Present illness:* Ten months before admission patient developed a sore throat which was soon followed by a productive cough. He began to lose weight and two months ago suffered from increasing weakness, pains in his chest and night-sweats. X-ray of his chest showed tuberculosis and patient was sent to Bellevue for one week, then transferred to Presbyterian Hospital. *Physical examination:* Showed a fairly well-developed and well-nourished young man. *Lungs:* Dulness, bronchovesicular breathing and medium moist râles were heard over the right apex anteriorly and posteriorly. Temperature 98.6° to 101.8°. Pulse 82 to 120, respirations 18 to 28. Weight 117, sputum positive for tubercle bacilli. X-ray of chest showed a diffuse mottling scattered throughout upper half of right lung and middle third of left. Both apices were clouded, especially the one on the right. Some of the shadows are fairly well calcified.

Diagnosis: Bilateral pulmonary tuberculosis.

Course: During 11 weeks in the filtered-air chamber the patient gradually

felt better. The temperature slowly assumed a lower range, from 98.6° to 100.2°; pulse ranged from 80 to 116; respirations 20 to 22. Weight increased from 117 to 128¾. The lung signs remained the same. X-ray of chest showed practically no change except a very slight amount of clearing of the process in the left lung.

COMMENT

The first two cases showed no improvement except for a very slight gain in weight. The third case showed more gain in weight and a decreased temperature and pulse range but not any greater than one would expect from 11 weeks' rest in bed. Stereo X-rays of the chest in the first two cases showed a slight increase in the process. In the last case the infiltration was noted as essentially unchanged with a slight possible decrease on the left side.

The patients were kept at bed-rest. They were given a high-caloric diet and symptomatic medication when it was required for cough or bowel movements.

The chamber was operated with all the precautions employed in oxygen-chamber therapy. Entering and leaving the chamber was done behind a rubber curtain so as to prevent the access of outside unfiltered air. The chamber was leak-tight. All air entering it was passed through the filter so that maximal filtration of dust and bacteria was achieved. The negative results that were obtained in these three cases of active bilateral tuberculosis appeared to indicate that the removal of air-borne bacteria is without influence on the maintenance of pulmonary tuberculosis.

CONCLUSIONS

A leak-tight room was equipped with a ventilation apparatus capable of passing the entire cubic contents of the room through a fine wool-filter each minute. After the air was filtered of 99 per cent of the dust and bacteria contained in it, it was passed over cold pipes for cooling and condensation of the moisture contained in it, and then heated so that optimal conditions of temperature and humidity prevailed in the room. Treatment with filtered air in this chamber was carried out in three cases of active bilateral pulmonary tuberculosis for a period of 11 weeks. No specific effects due to the inhalation of filtered air were observed. The patients responded as might be expected from rest in bed.

The author wishes to express his indebtedness and appreciation of the help of Dr. J. Burns Amberson, Jr., who selected the cases from Bellevue Hospital and observed them before and after treatment.

REFERENCES

(1) Storm van Leeuwen, W.: Therapeutics and Pharmacology, Proc. Roy. Soc. Med. of Lond., 1924, 1725.
Pathogenesis and therapy of bronchial asthma, Münch. med. Wchnschr., 1926, lxxiii, 599.
Results of treatment of bronchial asthma in room free from allergens, Klin. Wchnschr., 1926, v, 691.
Allergen-proof chamber in treatment of bronchial asthma and other respiratory diseases, Lancet, 1927, i, 1287.
(2) Leopold, S. S., and Leopold, C. S.: Jour. Am. Med. Ass., 1925, lxxxiv, 731.
(3) Cohen, M. B.: Clin. Med. & Surg., 1927, xxxiv, 276.
J. Lab. & Clin. Med., 1927, 1359.
(4) Rappaport, B. Z., Nelson, T., and Welker, W. H.: Jour. Am. Med. Ass., 1932, xcviii, 1861.
(5) Storm van Leeuwen, W.: Beitr. z. Klin. d. Tuberk., 1928, lxviii, 703.
Arch. Int. Med., 1930, xlvi, 637.
(6) Personal communication.
(7) Public Health Bulletin, no. 144, Treas. Dep't., U. S. Pub. Health Serv., Wash., D. C., 1925, p. 29.
(8) Owens Jet apparatus, C. T. Casella and Company, London.
(9) Gye, W. E. K.:
Brit. J. Exper. Path., 1922, iii, 241.
Public Health Reports, U. S. Public Health Serv., reprint 990, 1925, p. 291.
Public Health Bulletin 187, Treas. Dep't., U. S. Pub. Health Serv., 1929, pp. 1–206.

THE SANATORIUM TREATMENT OF LUPUS

LOUIS ALPERT[1]

That lupus is one of the most obstinate skin afflictions to treat is a fact every physician appreciates. Without exaggeration, practically every ointment, salve, chemical and physical reagent known has been tried some time or other, locally or generally.

In this paper, I wish to deal briefly with the sanatorium treatment in the care of these lesions.

Since 1925, the Lakeville State Sanatorium has been treating extrapulmonary forms of tuberculosis. Of the cases admitted, 30, or 3.36 per cent, in all showed skin lesions. Of these, seven showed other lesions, such as in lymph nodes, and involvement of the bones and joints. In the remaining twenty-three no other tuberculous lesions could be demonstrated. In 6 cases the tubercle bacillus was identified, either from discharges or scrapings, but the diagnosis is usually made on the character of the lesion and positive tuberculin tests.

As to sex, cases were about evenly divided, and, listing them according to age, one finds the greater majority in the first three decades of life, one-half of them between ten and thirty. The nose and face were the most common sites of attack; however, other parts of the body were not exempt. The more extensive lesions were found to start on the face, and spread down the neck, shoulders, arms and chest. Some showed small isolated lesions over various parts of the body, such as the trunk and both upper and lower extremities. This distribution is more common in children. One girl showed the distribution limited to the lower part of the legs, whereas the most extensive distribution is on a patient still in the sanatorium. He shows involvement of the entire face, ear-lobes, neck, axillae, chest, buttocks and legs. A conservative estimate of the extent of his active and healed lesions would place it between one-sixth and one-fourth of the entire skin surface of the body.

The general sanatorium treatment that these patients receive at first varies but little from the treatment for other extrapulmonary lesions; namely, rest in bed, three wholesome well-balanced meals a day, and

[1] Lakeville State Sanatorium, Middleboro, Massachusetts.

graduated periods of sun exposure to the entire body. We have no hard and fast rule as to the direct exposure of the lupus lesion to the sun. This varies with the case. As a rule, most lesions are benefited by the direct exposure. We have observed that the active lesion is apt to be irritated by the sun's rays, but the lesion that has become quiescent more frequently benefits by it. The best test is the clinical one. If the exposure to the sun shows results, such as bleaching of color and formation of scar-tissue, then continue with it; if, on the other hand, it causes increased erythema, spreading, and irritation, then withhold further exposure and try again at a later time. This applies only to the local exposures. The patient at all times continues to receive graduate periods of exposure to the rest of the body, starting with five minutes and working up to a maximum of one and one-half hours twice daily.

This by no means constitutes all the treatment. Any other therapeusis that may be indicated is tried. Bland salves are used for irritation, and salycilic-acid ointments to remove the dry and hard scabs that are apt to form, particularly on the lesions of the face and nose. We find this preferable to peroxide for removing crusts as the latter often produces irritation and induration.

Other supplementary treatments are employed as indicated. One patient, with a low basal-metabolism rate, was put on thyroid extract, to raise her rate to between plus 10 and plus 15, with marked beneficial results. Another whose lesions showed secondary infection, with sinus-formation and prolonged purulent drainage, was given two courses of vaccine treatment corresponding to the predominating organisms, with remarkable effects. The treatment improved his appetite, increased his weight, healed several of the sinuses and showed greatly diminished drainage of the others.

A most helpful reagent is acid nitrate of mercury, 50 per cent concentration. This is applied locally and in small amounts, similarly as nitric acid is applied to benign growths. Care must be taken not to let it run on healthy, surrounding tissue and that not too great an area be treated at one application, as it causes sloughing, and the local reaction may be severe enough to produce marked oedema and rise in temperature. We have found it especially helpful in the dried, hard, raised and glistening type of *tuberculosis cutis*, as this form is very resistant to all other methods of treatment. As many as 6 applications over the same area are sometimes necessary to destroy the pathological tissue deeply enough to reach the healthy underlying structures and produce healing scars.

Whereas local treatment may also have played its part, too much emphasis should not be placed on it in considering the results of our cases. We must bear in mind that the great majority of these patients have been using local applications for months and years, have tried every official and nonofficial remedy on the market, and have made the rounds of every large hospital and clinic before finally coming to a sanatorium as a last resort. One patient in particular went to the clinics for fifteen years, trying every form of therapy suggested before finally coming to the sanatorium for general treatment. Except for children and young adults, the majority of the patients treated come with a history of long duration. The longest was thirty-five years, and many were between five and fifteen years.

The unusually long duration of the illness and the fact that most of the patients have for years been treating their lesions locally, before enrolling in the general sanatorium regimen, should be borne in mind in reviewing the results of the sanatorium treatment of lupus.

The cases discharged were classified as unimproved, improved and arrested. The unimproved showed no progress. Those who showed definite healing yet insufficient to become rid of every trace of the lesion were considered improved, whereas the cases considered arrested were those whose lesions were replaced entirely by healed, bleached scar-tissue and which showed no other traces of inflammation and induration.

Table 1 presents the results obtained with the 30 cases treated. We notice that nine left against advice before giving the treatment a fair and sufficiently long enough trial. Of these I shall speak later.

Table 2 classifies the *arrested* cases as to age and length of the treatment period. We note that the younger patients fall in this group. We also find that the duration of illness is much shorter as compared with the improved group.

Table 3 lists the improved cases, and we find that the patient is much older, the duration of the lesion longer, and the stay in the sanatorium much shorter. Many of these patients left too soon, and there is no doubt that some might have been discharged as arrested had they stayed long enough.

Those who left with their lesions not improved bring out the above facts more clearly; namely, they are the older patients; they have had their lesions the longest and show the shortest residence. When a patient, who has had his condition for as long as ten to fifteen years, having most probably tried many and various forms of local and home treatment,

TABLE 1

Cases treated	30
Results	
Arrested	9
Improved	6
Quiescent	1
Discharged against advice	9
Still at sanatorium	5

TABLE 2

Arrested cases

AGE	LOCATION OF LESION	LENGTH OF STAY
3	Face	7 months
3	Face	7 months
4	Extremities	3 months
7	Face	20 months
12	Extremities	23 months
12	Body	12 months
15	Nose and face	27 months
15	Face and chest	21 months
20	Glands and face	12 months

TABLE 3

Improved cases

AGE	DURATION OF ILLNESS	LENGTH OF STAY
14	4 years	20 months
21	2 years	1 month
23	2½ years	8 months
26	6½ years	2 months
54	25 years	6 months
57	1 year	2 months

TABLE 4

Unimproved cases

AGE	DURATION OF ILLNESS	LENGTH OF STAY
20	13 years	3 days
23	2½ years	8 months
32	15 years	7 months
49	35 years	2 months
42	10 years	21 days
57	1 year	3 weeks

FIG. 1

FIG. 2

FIG. 3

FIG. 4

FIG. 5

FIG. 1. Age 17. Onset at five following cervical adenitis. Has had X-ray exposure and various forms of local treatment but lesion continued to spread. Has been proved tuberculous by biopsy.

Note the extent of the lesion and its verrucous character.

FIG. 2. Early lupus of nose and face. Age 24. Onset October, 1930. Began to improve three months after admission.

Note the healing, with scar-formation over nose and lip. On admission (November, 1931) the entire area was similar to the rough moist scabs of the left naries.

FIG. 3. Lupus of nose and face. Age 18. Before admission patient had locally X-rays, ultraviolet, fulguration and carbon-dioxide snow. Admitted to Lakeville State Sanatorium, July, 1929.

Note the healing that has taken place over the left cheek and upper lip, with the formation of smooth, bleached cicatricial tissue.

FIG. 4. Age 24. This patient had surgical scrapings of his lupus February, 1930. Scars are markedly injected and many pedunculated scabs have been removed since then. Several other lesions have appeared on other parts of the body.

FIG. 5. Same as fig. 4. Other side of face.

comes to try another form of treatment and stays for only a month or two and decides that the new treatment is not as miraculous as anticipated, the results that he has obtained should really not be considered as of any significance.

This leads to the discussion of recommending sanatorium treatment to lupus patients.

The reason that 9 patients left against advice is that they did not come to stay and give it a fair trial, but came because they had tried every other form of treatment, had exhausted all of their finances and every available source, or else had tired of going from clinic to clinic. They came, not with the attitude of staying long enough to judge whether or not this new treatment would result favorably, but with a tolerant and condescending feeling toward something different. Very often it is at the request and urging of the family or the family physician. Those who must stay because there is no other choice invariably profit from their long residence. This may be another reason why children obtain the best results. The independent adult soon becomes impatient and drifts on as he has done before.

One way of overcoming this is for the physician, social-service worker or clinic, that is sending the patient, to impress upon him that he has tried every other form of treatment and it has been found wanting, that the disease, because of its nature, is a chronic one and that the nature of sanatorium treatment is such that it takes many months before its beneficial affects can be felt.

Recently a young man was admitted with lupus of the nose and face. Prior to his admission he spent a year and a half in general hospitals receiving treatment. When, in spite of the scrapings, diet, light, and salves that he received, the lesions continued to spread and when his money gave out so that he could no longer pay for it all, he was convinced under high pressure to try sanatorium treatment. After staying three weeks he suddenly decided to leave because the lesion was still present. In the course of conversation he stated that he was shown pictures of patients "before and after" entering the Sanatorium and thought all he had to do was just report and similar fortune would await him, but he was not told that such results demand time and a great deal of it. Because he was helpless financially he stayed on, and, incidentally, after a few months, is now beginning to see convincing improvement.

It is true that forceful arguments may at times have to be resorted to to convince the patient of the desirability and necessity of treatment

away from home. However, considerable anxiety and disappointment on the part of the patient would be obviated, if the possibilities and limitations of sanatorium treatment are kept in mind.

These, judging from our results obtained are (1) younger patients respond more favorably to this form of treatment; (2) the sooner the treatment is instituted, the more complete is the cure; (3) the period of residence is, of necessity, long, and startling results should not be expected in the first few months; (4) the older patients should plan to stay at least a year before judging results; and (5) sanatorium treatment if begun early and continued will often prove effective in healing cases of lupus that were obstinate to the routine out-patient or office treatment.

SUMMARY

1. Thirty cases of lupus vulgaris treated at the Lakeville State Sanatorium are reviewed.

2. A relation between the age of the patient, duration of the lesion, length of residence and results of the treatment was noted.

3. The prognosis is better in younger patients and when the lesion is of shorter duration.

4. Sanatorium treatment is often effective after other methods have failed.

5. The residence is a long one and the treatment must be persisted in if good results are expected.

SOME ASPECTS OF ARTIFICIAL-PNEUMOTHORAX TECHNIQUE

With a Description of Two Improved Apparatuses[1]

J. W. CUTLER

Artificial pneumothorax may be considered to-day as one of the most important therapeutic procedures in the treatment of pulmonary tuberculosis. It is, therefore, desirable that the technique be standardized and apparatus improved wherever possible. With this in mind I have attempted to describe within the limits of a few pages some new and some little-used methods and devices that seem to me to be particularly useful.

NEEDLES

The literature abounds in descriptions of various needles advocated for artificial pneumothorax. Most of them are too long and too bulky and inflict unnecessary damage upon the pleura. A size that I have found most convenient for the average patient is a 20-gauge, 2-inch stainless steel needle with the standard Luer tip (figure 1). When the chest-wall is unusually thick a $2\frac{1}{2}$-inch needle of the same gauge may be used. The average thickness of the average chest-wall in its posterior aspect is less than 3 cm. and the 2-inch needle is sufficient. Longer needles are awkward to use and may break off. Needles of larger calibre cause unnecessary damage to the pleura. Finer-calibre needles may be clogged with blood. I use the 2-inch, 20-gauge needle with a medium-sized point for all inflations, including the initial one, and have found it safe and practical. I see no occasion for the use of an iridectomy knife at any time. A hypodermic needle for the first prick of the skin and a small quantity of novocaine intracutaneously not only will make all subsequent use of the pneumothorax needle painless, but the little wheal formed by the injection will serve as a very convenient marker for the introduction of the pneumothorax needle.

[1] From the Henry Phipps Institute of the University of Pennsylvania, Philadelphia, Pennsylvania.

THE TWO-WAY VALVE

Generally speaking, there are two methods available for the inflation of air or nitrogen into the chest-cavity, the open and the closed. The open method is the oldest and perhaps the most frequently employed. However, it involves unnecessary manoeuvres and increases the danger of infection of the pleura from exposure of the chest-cavity. In this technique the needle attached to a syringe is first pushed through the chest-wall into the pleural cavity. The syringe containing the anaesthetic is then removed and the rubber tube leading to the pneumothorax apparatus is attached to the open end of the needle.

The closed method involves the use of a two-way stop-cock (figure 1) between the needle and the syringe. The stop-cock is also attached to the pneumothorax apparatus. By turning the handle of the valve to the desired position, novocaine can be introduced, air injected or removed, fluid aspirated or medication instilled without at any time exposing the

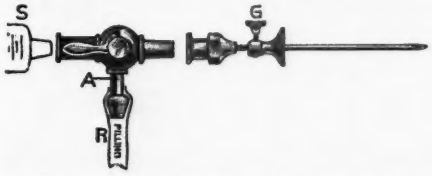


FIG. 1. PNEUMOTHORAX NEEDLE UNIT

With this unit air can be injected or removed, and fluid aspirated or medication instilled without at any time exposing the chest-cavity or changing needles.

S, syringe; A, two-way valve; G, movable guard; R, rubber tubing leading to pneumothorax apparatus.

chest-cavity or changing needles. The technique is thus simplified and made as nearly "fool-proof" as is possible.

THE MOVABLE GUARD

The movable guard illustrated in figure 1 serves a useful purpose, particularly for beginners. After the point of the pneumothorax needle has entered the pleural cavity for the first time, the thickness of the chest-wall can be readily determined by adjusting the guard so that the flat surface rests on the chest. The distance in millimetres between the guard and the point of the needle serves as a permanent record of the thickness of the chest-wall. In all subsequent inflations the guard is adjusted to the desired distance, and the needle pushed through until the guard rests on the chest-wall. This prevents possible injury to the lung.

In spite of these advantages, I seldom use the guard, for it seems to me more desirable to develop the sense of touch and to know by this means at all times where the point of the needle is. Such experience is highly desirable and becomes invaluable when doing initial inflations. To depend on the guard too completely is likely to make one less careful.

Figure 1 illustrates the assembly of a standard glass syringe, the two-way stop-cock, pneumothorax needle and movable guard into a complete and workable unit, making possible the inflation of the chest by the closed method described above. For each refill a different needle is used, but the rest of the unit is not changed.

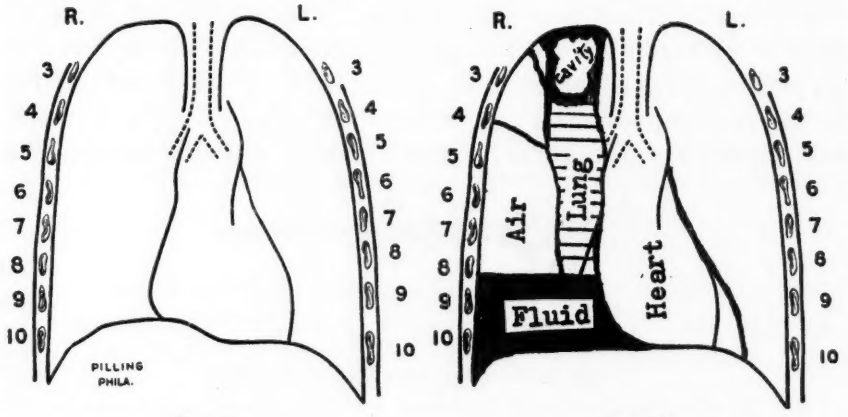


FIG. 2a FIG. 2b

FIG. 2a. Handy rubber stamp for recording fluoroscopic observations during the course of pneumothorax treatment.

FIG. 2b. Any displacement of heart, accumulation of fluid or presence of adhesions is easily recorded.

THE USE OF THE FLUOROSCOPE

One of the biggest advances in the treatment of pulmonary tuberculosis by artificial pneumothorax is the use of the fluoroscope before each refill. When the object, as of all modern pneumothorax treatment, is selective collapse, that is, complete collapse of the diseased part and complete unction of the healthy part of the treated lung, fluoroscopic observation before each refill is an urgent necessity. By this means (fluoroscopic observation) one can tell the position of the lung, whether there is too much or too little collapse, the character and strength of adhesions, and the danger of spontaneous pneumothorax from peripheral cavities. Without such knowledge artificial pneumothorax becomes a mechanical

procedure requiring very little skill and almost no judgment. With routine fluoroscopic control, artificial pneumothorax is an art requiring the best that one can give to his specialty. Needless to say, the pneumothorax operator should become thoroughly familiar with the use of the fluoroscope and should make his own observations and deductions. Artificial pneumothorax is far too important a treatment to be carried out by any but a thoroughly trained man.

Figure 2a illustrates a handy rubber stamp that I have designed for recording fluoroscopic observations during the course of pneumothorax treatment. Any displacement of the heart or accumulation of fluid is easily recorded (figure 2b). Thus a permanent record is obtained between roentgenograms.

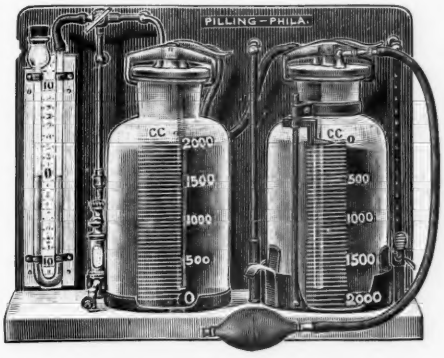


FIG. 3. CUTLER-ROBINSON PNEUMOTHORAX APPARATUS
An improved two-bottle pneumothorax apparatus embodying many new features.

IMPROVED TWO-BOTTLE PNEUMOTHORAX APPARATUS

Certain modifications of the pneumothorax apparatus have been suggested by my experience. Figure 3 illustrates a new and improved model of the familiar Robinson two-bottle pneumothorax apparatus, perhaps the most widely used of all pneumothorax apparatuses.

Very briefly, the apparatus has the following new and improved features:

Only one stop-cock is used. By turning it to the desired position as indicated on the dial, air may be introduced or manometer readings taken at any stage during operation. The stop-cock is of suitable size and is easily handled. It is so constructed that it cannot stick.

A filtering device has been made part of the apparatus. By unscrewing the cap and adding a few drops of a suitable antiseptic such as 5 per

cent phenol or metaphen, the air is filtered, both in refilling the apparatus and when inflating the pleural cavity. Its value is obvious.

The rubber stoppers have been replaced by chromium-plated lids, because not infrequently the rubber stoppers were forced out when the apparatus was filled or when the pressure bulb was used. Similarly, wherever possible, all rubber connections have been replaced by chromium-plated tubing.

The movable bottle has been provided with an easier lifting device and its graduations begin with zero at the top, permitting direct readings. It also has an easily operated indicator to mark the fluid level at the beginning of each operation. Both bottles allow unobstructed vision.

The water manometer has specially designed traps at its open ends (only one is shown in the illustration) to prevent escape of water from the manometer under various conditions, a not inconsiderable source of annoyance at certain times. The figures on the water manometer are large and clear.

A new locking device has been added to the pressure bulb and the rubber tube attaching to the pneumothorax apparatus, to prevent the possibility of the connections leaking or giving way.

AN IMPROVED PRESSURE PNEUMOTHORAX APPARATUS

Figure 4 illustrates a new and improved model of the pressure pneumothorax apparatus first described by Captain R. S. Loving, Medical Corps, U. S. Army.

The original apparatus gained little popularity, partly because it was little known and partly because it had certain inherent defects that made it at times inconvenient and unreliable. I have endeavored to correct these and the present model is offered as a scientific, accurate, and highly practical instrument. It is designed expressly for bed-side use, where portability, accuracy and ease of operation are essential requirements, and is ideal for its purpose. The apparatus requires no fluid, is always ready for immediate use, and weighs less than 9 pounds including carrying case.

The actual operation of the apparatus is extremely simple. One valve controls inflations, chest-pressure readings and complete closure. To explain figure 4 more fully, directions for the use of this apparatus are described as follows.

To Charge or Fill: Turn valve *H* into horizontal position. Attach pump to valve *A*. Open valve *A* and pump. Continue pumping air into

the jar until the mercury column *F* records zero. Close valve *A*. The apparatus is now ready for use.

Taking Chest-Pressure Readings: Open valve *L*, controlling the water manometer, and turn valve *H* to right. Chest readings will now be registered in water manometer *G*. Negative pressure is registered above zero, positive pressure below zero.

Delivering Air to Pleural Cavity: Turn valve *H* slowly from right to left. Filtered air will now pass into the pleural cavity, and the mercury column *F* will rise. This column measures the air that has entered the pleural cavity. The valve *K* must be open to permit the mercury column to rise.

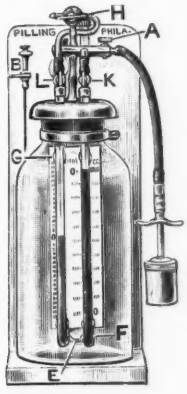


FIG. 4. CUTLER-LOVING PNEUMOTHORAX APPARATUS

A pressure pneumothorax apparatus designed expressly for bedside use, where portability, accuracy and ease of operation are essential requirements.

To Stop Delivery of Air: Turn valve *H* into neutral or horizontal position.

General Directions: The valve *A* should be open only while the container is being pumped up. The valves *K* and *L* should be open or vertical throughout the use of the apparatus, and closed when the instrument is not in use. The valve *H* is the main valve, and should be in neutral or horizontal position while air is being pumped into the container. It should be turned to the right when taking chest-pressure readings, and to the left for delivery of air into the pleural cavity.

The apparatus should be kept in an upright position, but with the valves *K* and *L* closed. It may be turned over without spilling mercury or water from manometers.

PREVI

It is c
we shou
Robert
true pio
exquisit
belong t
vey, Jer
I wish
pure cul
Cohnhe
time; hi
his proc
liquid g
the aeti
of infect
conjunc
which h
of *Rinde*
that dis
treatme
study of
before h
—each v
his *magn*
are inter
tion of
product

[1] The R
University

PREVENTIVE AND THERAPEUTIC MEASURES IN TUBERCULOSIS SINCE KOCH

A Brief Critical Review[1]

EDGAR MAYER

ROBERT KOCH

It is only fitting that, before taking up the subject of to-night's address, we should pay at least an introductory tribute to the great figure of Robert Koch, German master-mind of the science of bacteriology and a true pioneer in this field. Of a genius comparable to that of Pasteur, his exquisite skill and acumen have never been excelled. How truly does he belong to that immortal band of epoch-makers in medicine,—with Harvey, Jenner, Pasteur, Lister, Beaumont,—yes, with Vesalius!

I wish that I might elaborate here upon his great work:—the isolation in pure culture of the bacillus of anthrax and the study of its life-cycle, which Cohnheim declared to be the greatest bacteriological contribution to that time; his method of fixing and staining bacterial films on cover-slips; his procedures in obtaining pure cultures of microörganisms by spreading liquid gelatin with meat infusion upon glass plates; his great treatise on the aetiology of traumatic infectious diseases which placed the knowledge of infections on a firm footing; his discovery of the organism of infectious conjunctivitis; his identification of the comma bacillus of cholera by which he transformed the science of infection; his study of the nature of *Rinderpest* in South Africa and the finding of a means of combating that disease; his investigations of bubonic plague, and of the origin and treatment of malaria at Bombay, South Africa, and thereabouts; his study of sleeping sickness in East Africa as late as 1906, only four years before his death:—discoveries, all, of inestimable importance to medicine,—each work in itself outstanding, and yet insignificant in comparison to his *magnum opus*, the isolation and staining of the organism in which we are interested to-night, the *tubercle bacillus*, and the consequent formulation of his never-to-be-forgotten *postulates*, and the manufacture of the product of growth of the bacillus, *tuberculin*.

[1] The Robert Koch Lecture, read before the Alpha Omega Alpha Society and Syracuse University School of Medicine, Syracuse, New York, May 17, 1932.

It is true that Laennec, inventor of the stethoscope, following Bayle's investigations, first crystallized and described "anatomical tubercle," and that Cohnheim successfully inoculated tuberculosis into the anterior chamber of the rabbit's eye. We know how Klencke showed tuberculosis transmissible through cow's milk, how Celli proved that the infectious agent of tuberculosis retains its virulence and reproductive powers after passing through the intestines of flies, and how Villemin demonstrated tuberculosis to be a specific infection, due to an invisible agent transmissible by inoculation from man to lower animals.

But it remained for a young country doctor, with his opportunities for thought broken up by endless rounds of visits—a district physician riding over rough roads,— to glean sufficient hours for study from his practice, and in the short space of six months to complete this unparalleled study of the aetiology of tuberculosis.

Well may Ehrlich have remarked that our entire knowledge of infectious diseases and various related branches of learning rests upon the foundations which Koch established, for it was Koch who devised methods which gave science the possibility of solving problems of immunity on an exact experimental basis, and who taught the world how to transmit infectious diseases experimentally from animal to animal. When we realize that in this fashion he made it possible to apply therapeutic methods experimentally, we can see how subsequent work in connection with consumption and allied conditions rests upon his initial discoveries.

EARLY MEASURES OF TREATMENT

It is a brief step from the discovery of the tubercle bacillus in 1882 to the establishment of the first American sanatorium for tuberculosis, that of Trudeau at Saranac Lake, New York in 1884. It was only shortly after the description of the staining of this bacillus in the *Berliner Klinische Wochenschrift* that Trudeau patiently trod the steps of Prudden's laboratory in New York to learn the technique for identifying the organism. True it is that this first American sanatorium was founded upon the methods instituted many years before by Brehmer and Dettweiler in the treatment of tuberculosis. How familiar to all of us is the description of their early practice so often quoted, of assigning patients rest and also regulated *exercise in the out-of-doors,* walks up winding paths and hilly slopes, to strengthen what was then considered at least in part a congenital fault, namely, a relatively small and weak heart. But of course it was not many years before this conception was upset; and, in

turn, quick recognition was made of the falsity of the dictum of Niemeyer which had held sway for some few years, that "the worst that could happen to a consumptive was to become tuberculous."

Following close upon the recognition of the bacillus, came the announcement of the discovery of one of its products, *tuberculin*, a substance that aroused great hopes as an agent for curing the disease. Few remedies have been received with so much hope and have caused such bitter disappointments after such enthusiastic approval.

Although the history of the *specific tuberculin treatment* of *pulmonary tuberculosis* is not especially praiseworthy, still, its use as a means of *diagnosing the existence of tuberculosis in animals intended for food* has been found valid, and, as a *diagnostic procedure to reveal the presence of infection in human beings, it has* proved indispensable.

Koch tried it on himself and reacted to a dose of two centigrams. As a result, he unfortunately recommended this as the initial dose for treatment. His reaction to tuberculin, as his necropsy showed, was due to tuberculous changes in his lungs of which he had never been aware. It is possible that if Koch had had a more active tuberculosis and had reacted to smaller doses of tuberculin, the history of this treatment would read differently now.

The lack of an accepted interpretation of the phenomena observed in the tuberculin reaction has without doubt created strong opposition against its use. The toxin-antitoxin theory, or the cellular antibody reaction to toxins, the importance of cellular immunity in tuberculosis for production of specific antibodies when stimulated by the presence of antigen, the altered course of superinfections, the troublesome and, under certain conditions, fatal hypersensitiveness, are indeed related problems in the study of *allergy and immunity*. These are all limited perhaps by time and degree, operating, as Krause suggests, mechanically, either in one phase to fix tubercle bacilli at points of reinfection and thus prevent or retard their spread, or at other times to fail in checking their growth and act destructively against the host. During the allergic stage reinfecting bacilli may be destroyed by specific bacteriolysins, a mechanism through which increased resistance has been explained to act. Whether they play the major rôle in defense, or whether protection is brought about chiefly by the *monocytes* which have a lipolytic action and the *leucocytes* with their proteolytic action must yet be decided. The leucocytic infiltration may well be as concerned with the destruction of reinfecting organisms as the antibodies, not only by the setting up of me-

chanical barriers, but by their physiological action. Yet it is true that immunity may be as much or more connected with the tuberculous tissue as with the living tubercle bacilli, regardless of whether the causative factor is living or dead organisms, inasmuch as the only present requisite for tissue allergy and *relative immunity* is anatomical tubercle. *Dead bacilli alone produce transitory allergy and immunity.* All these and other problems in a vast network of complexity still confuse the group who are aiming to elucidate for us the problem of tuberculoimmunity. Their extensive experimental work is only now beginning to clarify the field of specific therapy by which exaggerated allergic reactions have been formerly produced, but which to-day may give place to the more rational method of desensitization. Will these workers elucidate why tuberculin therapy, in minimal dosage with avoidance of reactions, will heal haemorrhagic disease of the retina, and yet prove equally valuable in the healing of lupus vulgaris through the production of slight allergic focal reactions? Such problems compel attention to the whole immunobiological field.

We must ask ourselves whether we really are imitating nature by aiming to retain hypersensitiveness during Ranke's first allergic stage of the primary complex, and his second stage of hypersensitivenss marked by blood-stream propagation, while we ban his third stage of *relative anergy* from this treatment. Must we not rather revise our notions and agree with Rich that *desensitization* should be our aim? Can we predict that the establishment of immunity will be produced without the presence of tissue hypersensitiveness? Has it not been because of highly destructive allergy in exudative tuberculosis that we have all willingly avoided the use of tuberculin in this form? Rich has reported, but not published, that sensitized guinea pigs can be desensitized to tuberculin and still remain as immune as the allergic animals to reinfection. Are we to attempt the clinically troublesome problem of desensitization by tuberculin therapy to secure the added benefits undoubtedly to be obtained from a diminution of the well-known destructive effects of tissue hypersensitiveness, when we acknowledge that the desensitization of these experimental animals produces a marked emaciation and often their death? Such difficulties force us to consider whether a change of viewpoint in tuberculoimmunity will offer a new basis for specific therapy.

Close upon the era of tuberculin treatment came the extended period with the use of the *whole body of the bacillus*, not only of *dead organisms*, but even of the *living*. It is sufficient merely to refer in passing to the use of living attenuated organisms, such as Friedmann's turtle bacilli, acid-

fast members of the timothy group, smegma, avian and bovine bacilli, and finally the heroic administration of single numbers of living and virulent human tubercle bacilli.

These and the passive immunizing measures with the many forms of sera and even the use of transfused blood from immune donors can only be referred to from the standpoint of failure.

The many forms of chemotherapy in tuberculosis to-day present volumes of literature; the use of iron, copper, mercury and other metals has been carefully tried. For the most part, the use of these, as well as that of such derivatives as of codliver and chaulmoogra oils, has been set aside. Sanocrysin and other gold compounds still hold their proponents, but results still hang in the balance.

PREVENTION

Only the briefest reference can be made here to such well-known successes of the public-health measures as sanitation; compulsory legislation as to sputum disposal; registration of consumptives; development of preventoria and sanatorium treatment with its segregation of patients; the Grancher system for the farming out of children of tuberculous parents; the campaigns for early diagnosis; the enforcement of pasteurization of milk and the tuberculin testing of cattle. The value of these measures needs no defense. For example, pasteurization of milk now available in Massachusetts for 60 per cent of the population is considered a prime reason for the reduction of the incidence of tuberculous infection which was formerly so widespread in that State. With a marked decrease in the number of infected persons, as well as with the increase of adult negative reactors who were previously positive, tuberculin tests become of diagnostic value for exclusion in adults. These tests should also aid in studies of the problem of adult exogenous reinfection, as indicated by reports of Myers and others on medical students and nurses.

The lack of enforcement of pasteurization of milk in England is partly responsible for the high incidence of bovine tuberculous infections there. The case for Scotland is even worse. In these countries, bovine infection accounts for 45 per cent of tuberculous cervical lymphadenitis, 48 per cent of lupus, 30 per cent of tuberculous meningitis, 18 per cent of bone-and-joint tuberculosis and 17 per cent of genitourinary tuberculosis. In Scotland, even pulmonary tuberculosis due to bovine infection reaches 4 per cent, all this despite the declaration of the great master Koch thirty years ago in London that human infection with bovine bacilli was so rare

that measures against it were not deemed necessary. Household sterilization of milk is not likely to be properly done or rigidly followed out, and health authorities should certainly be compelled to enforce pasteurization of all milk from untested cows.

The field of prevention is to-day so strongly organized that we can favorably predict a continued drop in tuberculosis mortality. I refer particularly to the organized efforts now made for the detection of tuberculosis in children of school age through complete physical examinations, tuberculin tests, X-ray studies and temperature records, laboratory search for tubercle bacilli not only in sputum, but in gastric contents and stools. Such studies have already indicated a 3 to 4 per cent incidence of childhood tuberculosis and 0.7 per cent of the adult form of tuberculosis that would in part have been unrecognized. That perhaps 50 per cent of all adult tuberculosis may develop from the 3 or 4 per cent of children detected with the childhood type of disease is suggested. Ten per cent of the children of tuberculous families show manifest disease, and they are four times as likely to develop childhood tuberculosis as the noncontact children, and twice as likely to have the adult type of tuberculosis. Calcified lymph nodes of the tracheobronchial region are found in them five times as often as in the unexposed children. Statistical studies are not yet sufficiently complete to permit a generalization that the existence of a previous infection in children either predisposes to or protects them from subsequent active disease. The work of Opie and MacPhedran among medical students in Philadelphia will in due time probably provide a basis for evaluating these factors.

The status of the immunizing action of the *Bacillus Calmette-Guérin* still presents much controversy. The possibilities of the transmutation of this living bovine bacillus to a virulent microörganism, through a change of culture medium or through dissociation in the host, still has its proponents. Virulent organisms produced from *BCG* cultures are claimed by their demonstrators not to be contaminations of human origin. The opinion that there are many intermediate types of tubercle bacilli, that cannot be differentiated as either strictly human or bovine through the formerly accepted animal tests, makes evaluation more difficult. Dissociation of *BCG*, as well as of avian cultures, into virulent types has been shown to occur in artificial culture media, but not in the human body. The dangers cited in the use of this method of prevention of tuberculosis in children must yet be substantiated. On the other hand,

proof of a lasting immunity from its use is lacking and the many statistical studies are faulty. We cannot admit that the results of this prophylactic immunization, quoted as so favorable, have been proved.

The use of dead tubercle bacilli (killed by heat) for producing hypersensitiveness and relative immunity that can be shown to last for from 12 to 18 months presents no risk; and its possibilities as a transient immunizing agent should make us hesitate to adopt such a generalized use of live bacilli as has been carried out abroad.

THE THORACIC CAGE AND MEASURES OF REST

Rest and fresh air have completely withstood the tests of time and remain our sovereign remedies. And so there have followed in line such important surgical measures of treatment intended to immobilize the lung as artificial pneumothorax and its adjuvant procedures of intrapleural pneumolysis and oleothorax; *thoracoplasty*, extrapleural pneumolysis, *phrenicectomy*, scaleniotomy and similar operations. A reluctance to apply active and radical measures in the treatment of pulmonary tuberculosis has been marked up to recent years. However, the good results of pneumothorax treatment paved the way for more radical surgical methods, aimed to give well-selected patients, who would be otherwise hopeless cases, a chance to be practically cured. The aim of thoracic surgery from the start was not so much an anatomical as a functional amputation of the diseased lung. The mechanism of operation was soon taken into consideration. Sudden effects on respiration and circulation have been carefully evaluated, with due attention given to mediastinal flutter, sputum retention, aspiration pneumonia, toxin crisis, and so forth.

With the constantly improved methods of operative technique, can we look forward to a further reduction of mortality, with a better selection of properly suited cases, not only for pneumothorax but also for phrenicectomy and thoracoplasty? It is possible that, in the past, operations have been used as a last resort in too many cases that were hopeless; and that, on the other hand, many suitable cases that could have been saved have not been selected for surgical treatment. Have we, in the selection of cases, properly taken into account the pathological-anatomical nature of the tuberculous lesion, as well as the physiology and pathology of respiration and circulation? We do not believe that we have. The differences in the conceptions of various workers concerning the clinical-

pathological states of the diseased lung are to-day too great, and do not sufficiently conform to uniform standards, to allow the internist and the surgeon accurately to define indications for interference and to compare statistical results properly.

The treatment of advanced pulmonary tuberculosis is to a great extent the treatment of cavities, although we of course recognize the existence of far-advanced disease without cavity. The menace of a patent cavity and positive sputum, with its great possibilities for bronchogenous spread, haemorrhage and other dissemination, has not been given sufficient thought. The ideal treatment of cavity should be complete obliteration.

The bacillus-carrier problem in tuberculosis should receive more attention from this standpoint. It does not seem logical to treat a chronic infectious disease during the active, progressive stage only, and to ignore the presence in the body of the tubercle bacillus before and after that period.

The reports from municipal hospitals bear out the fact that the persistence of cavity in a public charge apparently spells a fatal termination. It sounds surprising to hear that Barnes and Barnes, who studied the outcome of 1,454 cavities (probably in consumptives with far-advanced disease), found as high a mortality as 80 per cent within a year and 90 per cent within five years, with an average duration of life of only 15.8 months. However, on the favorable side, our own figures speak emphatically, for in a study of pneumothorax treatment of 124 patients, four years after reëxpansion, 67 were healed and cavities were closed, of whom 82 per cent had regained and retained their working and earning ability; while, of 57 patients with cavities partially closed and having rigid walls, only 33 per cent were living and 30 per cent were able to work. As to the duration of pneumothorax, cavities collapsed over two years gave us the best end-results. Furthermore, analysis of end-results with cavity will demonstrate that the character and extent of the surrounding and accompanying pulmonary disease influence prognosis more than the cavity itself. Minimal disease with cavity can be compatible with long life.

Yet, in the treatment of early pulmonary tuberculosis, should we not discourage the indiscriminate use of these surgical measures at the very onset? Should we not restrain our enthusiasm and discount the over-optimistic reports in behalf of immediate interference when we realize what rest alone may do at times, not only in rapidly clearing up acute

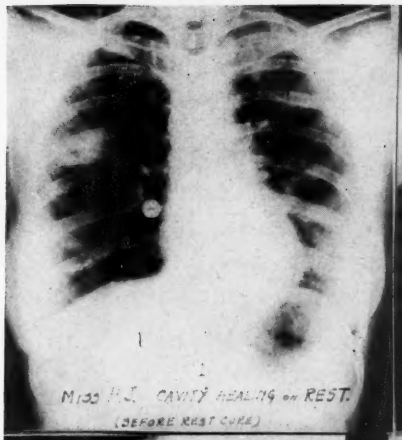


FIG. 1A

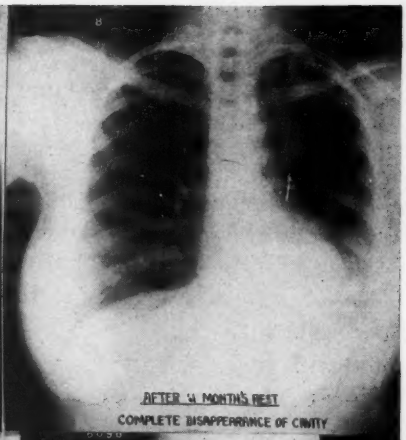


FIG. 1B

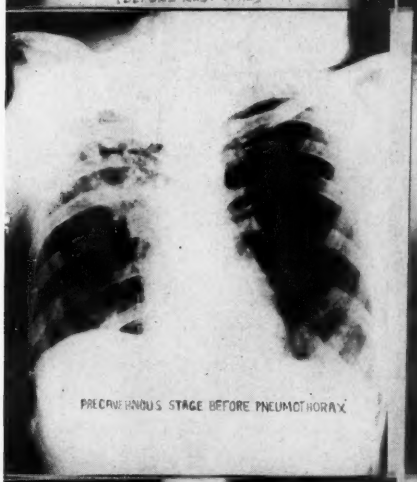


FIG. 2A

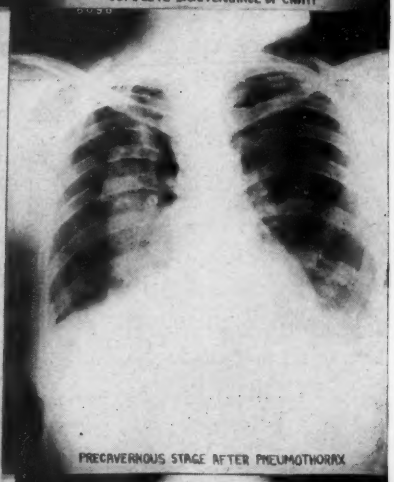


FIG. 2B

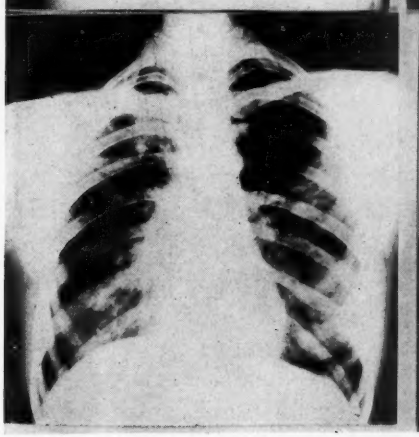


FIG. 3A

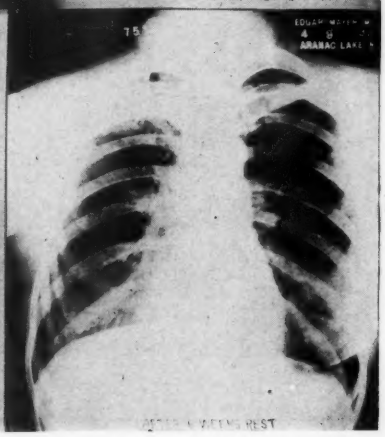


FIG. 3B

FIG. 1

A: Cavity (left lung) healing on rest (before rest cure).

B: Cavity healing on rest (after four months). Complete disappearance of cavity.

FIG. 2

A: Precavernous stage (before pneumothorax).

B: Precavernous stage (after pneumothorax).

FIG. 3

A: Elastic cavity (right lung), disappearing on rest (before rest).

B: Elastic cavity, disappearing on rest (after six weeks' rest).

tuberculosis probably produced on a highly allergic soil, but even in causing complete disappearance of elastic-walled cavities? Will not an unbiased analysis of our results with pneumothorax therapy and with phrenicectomy reveal that our enthusiasm for the early institution of these measures is due in large part to the disappearance of the two forms of disease just mentioned? In a personal study of twenty-two such cavities treated with bed-rest only, eleven have completely disappeared and five were greatly decreased in size in as brief a period as five months. In the pseudocavernous forms of disease (if we can term it such), as indicated by X-ray, in which one has dared to assume theoretically that the annular shadow made out is not a true wall but is composed of closely packed layers of cells bordering an area of infiltration which has not yet progressed to caseation, or where it has been suggested that resolution has already taken place in the centre but not at the periphery, it is obvious that such a zone of demarcation can come and go rapidly and has been wrongly interpreted as a disappearing cavity. Such annular infiltration may progress to an early elastic cavity or to involution. It will usually respond well to pneumothorax and phrenic-nerve treatment.

The classification of cavities by Pinner and Fischel has correlated closely with that used by us in helping to define indications for treatment. Not the X-ray alone, but all facts, more particularly age and location of cavity, influence our evaluation of the pathology of cavities. The early thin or elastic-walled cavities, of round or *oval* contour, developing in early or late phases of the disease, are usually found below the clavicle toward the periphery and nearer to the dorsal surface of the lung, although they are occasionally found elsewhere. They show pathologically either a heavy perifocal infiltration and this border shades off into the normal tissue, or a *thin* clearly defined border, and both have a tendency to spontaneous obliteration, which can be explained by the elasticity of the surrounding pulmonary tissue, the softness of the walls, the absence of ridges and trabeculations, and, most important, a freedom from pleural adhesions. The actual loss of parenchyma is considerably smaller than the X-ray would indicate; a minimal of fibrotic reaction in the surrounding tissue results in a thin fibrous mantle replacing the elastic network. In healing, the surrounding infiltration absorbs, concentric retraction of the cavity can take place, and disappearance of a cavity may occur in a short time. These are probably the lesions that were formerly interpreted in Saranac Lake as localized pneumothoraces.

On the other hand, transformation into a thick-walled or rigid form may be the outcome. In this stage the irregularly sharp and dense-walled cavity shows marked fibrotic irregularities in the wall and is often accompanied by a pronounced pleural thickening. It is largely this pleural thickening, as well as the dense surrounding disease, that interfere with pneumothorax therapy. Fluid levels are not uncommonly seen which may often be correlated with impaired bronchial drainage. Here the chances for ultimate recovery and for disappearance of the cavity are decidedly worse, although the chances of the patient's survival are slightly improved. Healing, if it occurs, is rarely by collapse and apposition of the wall of the cavity, but by massive fibrosis, leaving, according to Pinner, a stellate scar, so different from the more linear scar occasionally seen in healing of the round cavity. Pneumothorax treatment and phrenic-nerve operations

FIG. 4. Elastic "round cavity"

for the elastic cavity can give excellent results, whereas, with the rigid cavity and its adherent pleura, such treatment less often effects a collapse, and cavities are frequently merely displaced and not sufficiently compressed to close.

Small multiple cavities, or honeycombing in densely infiltrated areas (often termed "moth-eaten"), represent localized loss of substance in areas of caseous pneumonia which are usually not located at the apices and represent a defenseless condition. With an absence of pleural thickening they indicate immediate collapse therapy; however, as few as 20 per cent will survive one year, according to the figures of Barnes.

It is evident that the elastic-walled cavity is the only one to show a tendency to spontaneous healing, and its final development is determined by changes in the surrounding infiltration. It is the cavity that often disappears under pneumothorax and phrenic-nerve therapy. Extension or

retrogression must be carefully watched for, if the measures of interference are delayed. The danger lies in development into the rigid-walled cavity, with which results of pneumothorax and phrenic-nerve therapy have been poor. Only by the application of additional surgical measures can the large rigid cavities be closed; and, even with such surgery, the

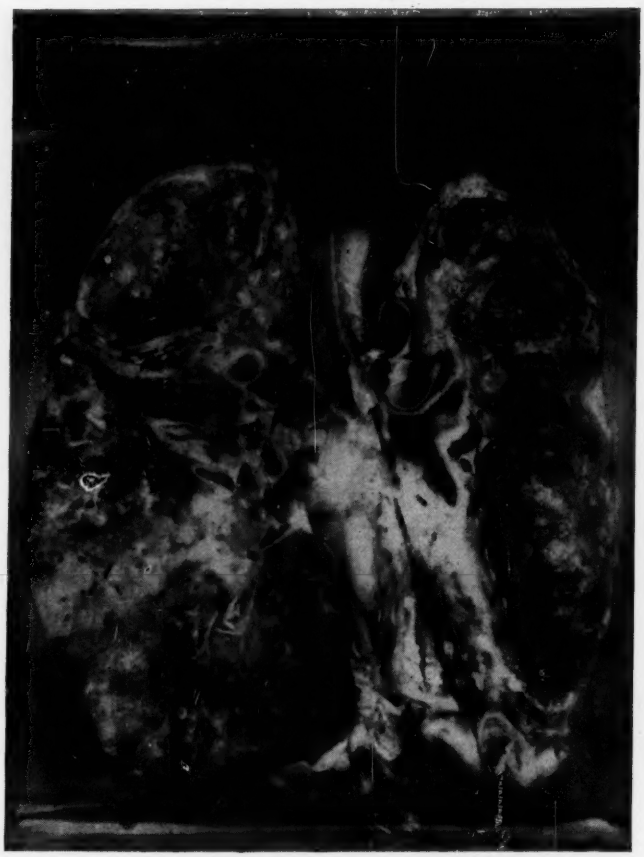
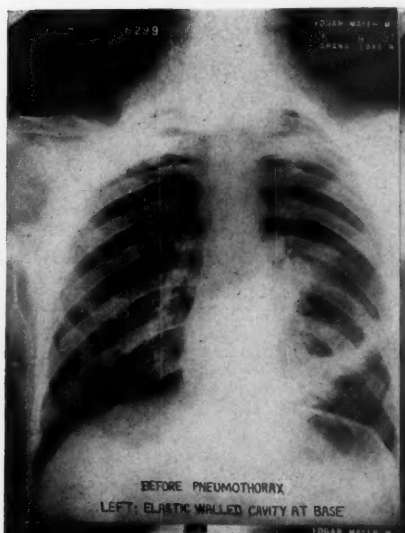


FIG. 5. Rigid or resistant cavities

rigid, adherent, thick-walled cavity still presents most disappointing results.

For the large rigid upper-lobe cavities should we not advise that thoracoplasty be instituted as an *immediate* measure of treatment instead of first attempting the production of pneumothorax? Especially is this so if extensive pulmonary involvement accompanies the cavity-formation,

FIG. 6A



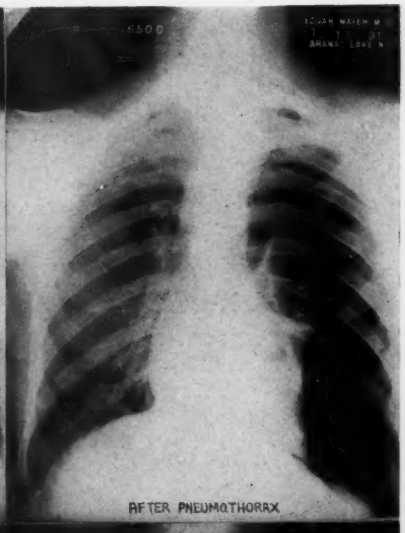


FIG. 6B

FIG. 7A

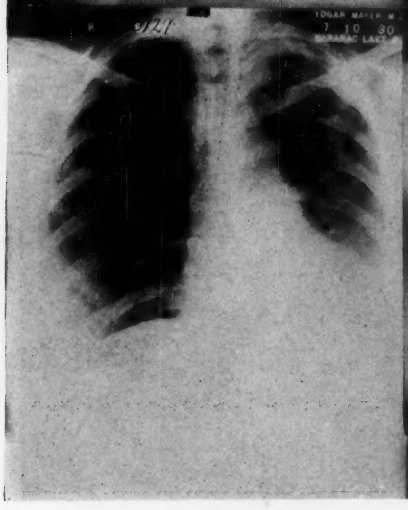


FIG. 7B

FIG. 6

A: Elastic-walled cavity at base that disappeared with pneumothorax (before pneumothorax).

B: Elastic-walled cavity at base that disappeared with pneumothorax (after pneumothorax).

FIG. 7

A: Large rigid-walled cavity that should have thoracoplasty done without attempting pneumothorax (before pneumothorax treatments).

B: Rigid-walled cavity resisting pneumothorax (after pneumothorax).

indicating a permanent loss of respiratory function of the involved lung; and, likewise, if we consider the danger of rupture.

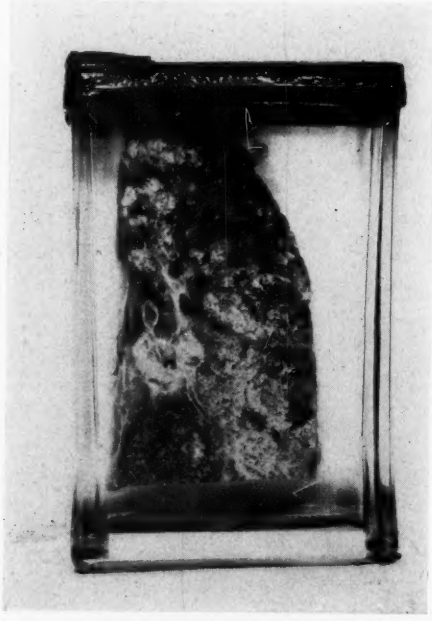


FIG. 8. "Moth-eaten" multilocular cavities (postmortem specimen)

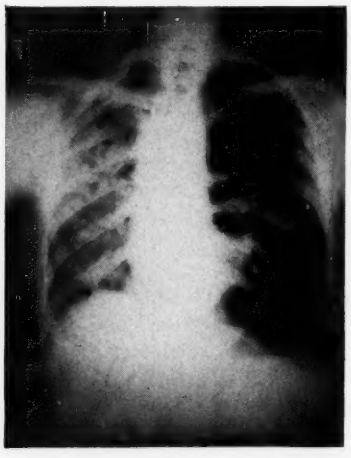


FIG. 9. "Moth eaten" cavity (X-ray)

That there are other cavities, such as the bronchiectatic, or the flat cavity of Alexander with narrow anteroposterior diameter, is clear; that

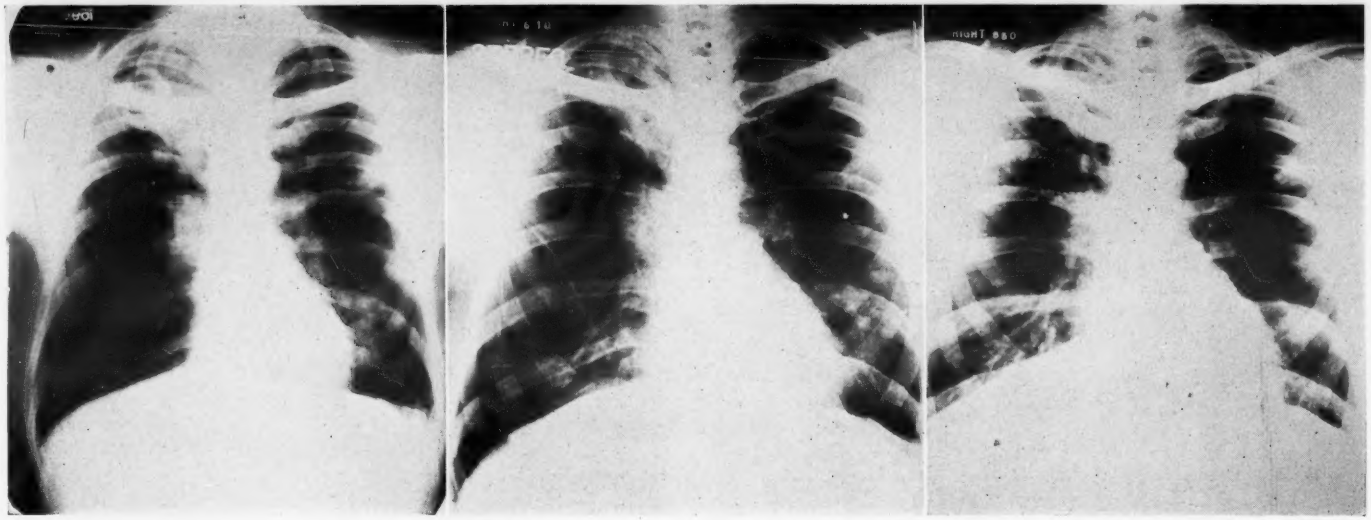


FIG. 10A FIG. 10B FIG. 10C

FIG. 10

A: Elastic cavity at apex; disappeared after 100 cc. of air in pleural space (before pneumothorax).
B: Elastic cavity at apex; disappeared (after pneumothorax treatment of 100 cc.). Note air is chiefly seen in pleural space at base.
C: Elastic cavity at apex; disappeared (lung reëxpanded).

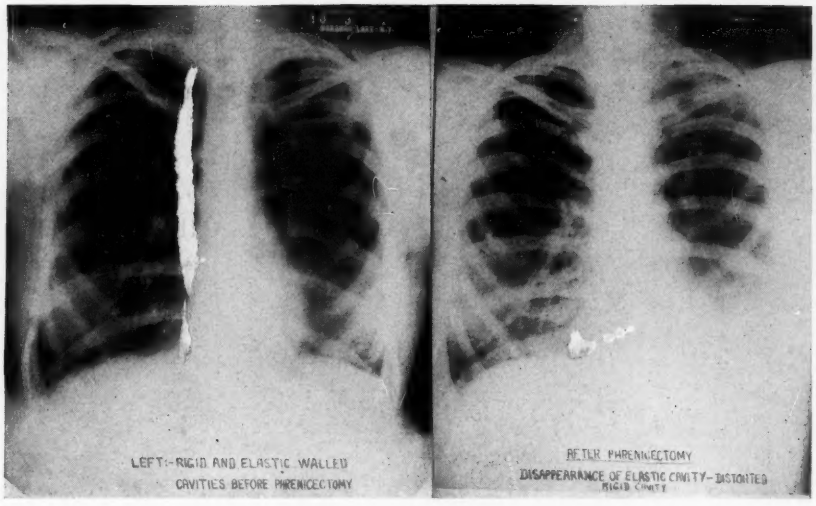


FIG. 11A FIG. 11B

FIG. 11

A: Rigid and elastic-walled cavities; left side (before phrenicectomy).
B: Disappearance of elastic cavity; distorted rigid cavity, left side (after phrenicectomy).

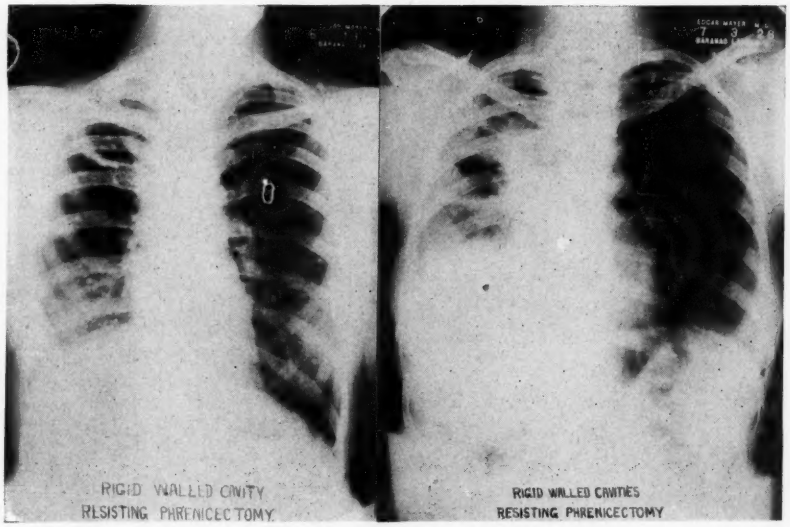


FIG. 12 FIG. 13

FIG. 12. Rigid-walled cavity resisting phrenicectomy
FIG. 13. Rigid-walled cavity resisting phrenicectomy

the outlook varies with their number and size and location as well as age is also evident; and that their healing may be explained by a production of closure of the bronchus with accompanying atelectasis and oxygen starvation of the bacillus must be given some consideration; that thick-walled cavities, in the depths and free from pleural involvement, can at times be compressed, while superficial elastic-walled forms with pleural adhesions are resistant to pneumothorax therapy is certain; and that not all cavities can be easily labelled by X-ray to conform to the types mentioned is recognized. However, better understanding of their development, as

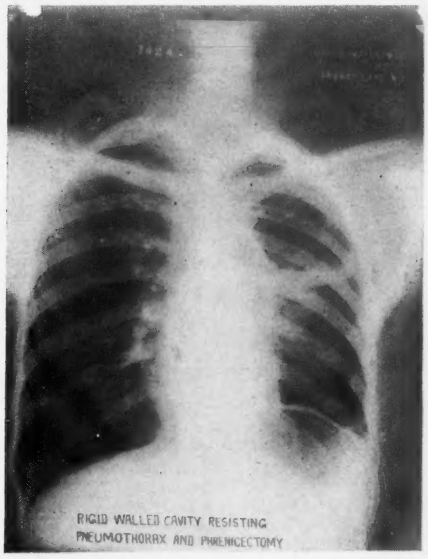


FIG. 14. Rigid-walled cavity resisting pneumothorax and phrenicectomy

well as the recognition and significance of the respective types, should point the way to better opportunities for appropriate and timely interference.

THE SOIL

Aside from these measures of direct attack upon the bacillus, have we directed adequate attention to the soil of the host? In this attack, have

[2] Attempts to close therapeutically the draining bronchus of a cavity by bronchoscopic instillation, as well as by direct injections of silver nitrate are suggested; but the whole question of the dynamics of the lung, the separation of stationary cavities from those that may continue to secrete and enlarge, and similar problems are still in want of solution.

we formed sufficient understanding of the chemistry of the cell and its reaction to the products of the bacillus? Can we not conceive that an environment unfavorable for the bacillus may bring about a lowering of its virulence through a dissociation leading to a predominantly avirulent form? Such factors as the partial pressure of the gases to which the bacillus is exposed, the hydrogen-ion concentration, and variations in the water balance may be among the important ones in determining both the development and the pathogenicity of the bacillus within the host.

Without a doubt, studies are constantly in progress to learn what factors of the actual disease can be produced chemically. Pure protein, one of the active parts of tuberculin, has been produced in crystalline form. Lipoids have been extracted from the bacillus, and studies have been made of the bacillary residue for proteins and carbohydrates. With the phosphatide extract, many characteristic lesions of the disease have been produced; although some evidence now indicates that these are due to bacilli within the lipin. Both specific protein and specific carbohydrate fractions have proved to be toxic to tuberculous animals. The comparative respiratory physiology of various members of the acid-fast group is being studied, to determine the foodstuffs essential for the growth of the tubercle bacillus. A single bacillus has been isolated by new methods and its entire life-cycle studied microscopically. Cultures grown from a single bacterial cell, the bovine bacillus, have been shown to dissociate into typical rough and smooth types of colonies; and their attendant differences, such as reproduction by budding in the rough type, and by fission in the smooth type, and their properties of motility, velocity of growth and varying pathogenicity are being defined.

Discovery of the physiological rôle of unusual inorganic elements, often effective in exceedingly small amounts, characterizes, in part, modern nutrition. About 5 per cent of the body consists of mineral salts, a large part being calcium and phosphorus salts of the bones. Importance of the biochemistry of such salts is found in such relationship as that of the pituitary to bony growth, the shift of calcium and phosphorus under parathyroid influence, and the failure of normal calcification in the absence of vitamine D.

The rôle of the *calcium factor* in tuberculosis must still be revealed. Recent crystallization of vitamine D has served to turn attention again to the physiological activity and the chemical transformations exhibited by this class of substances in the body. It remains to be explained why viosterol has not proved an aid in the healing of human pulmonary tuber-

culosis. It has been shown to influence favorably the deposit of calcium in experimental bovine tuberculous infection of rabbits and guinea pigs.

Whether calcium therapy in tuberculosis may play a part because of the chemical relationship of calcium to other ions and because of its pharmacological action, rather than as a basis of healing through depositions in caseous tissue, must receive some thought. Chemical examinations of the diseased foci of lupus vulgaris after dietary treatment in the nature of restriction of sodium chloride, limitation of protein and carbohydrate intake, and administration of calcium compounds and of foods rich

FIG. 15. Lupus vulgaris of face. Healing under special dietary after resisting all other forms of therapy.

in vitamines, have revealed, according to Doerrfel, distinct mineral displacements, sodium being greatly diminished, potassium increased, and histological studies have shown healed disease. Calcium, as an antagonistic kation to sodium, has been stressed in this form of therapy.

Whether the mechanism of the response of lupus vulgaris to this dietary is similar to the response to general exposures of ultraviolet radiation can only be theoretically conceived. Studies of the disappearance of the oedema and the purplish discoloration of active lupus strongly suggest the factor of altered capillary permeability, changed osmotic pressure and

blood-flow, a response that can well take place with both forms of therapy and their accompanying changes in mineral metabolism. However, one can only speculate as to such possibilities.

Why light energy will undoubtedly heal lupus vulgaris and scrofuloderma, but should have little or no effect upon lupus erythematosus and upon tuberculides; why it should help heal in many instances the chronic ulcerative form of intestinal tuberculosis and so rarely favorably affect the acute forms; why it should have such beneficial action upon peritoneal tuberculosis with ascites and rarely help the adhesive type; why it should play a significant rôle in the healing of the exudative synovial form of joint tuberculosis and be of minor value in comparison to ortho-

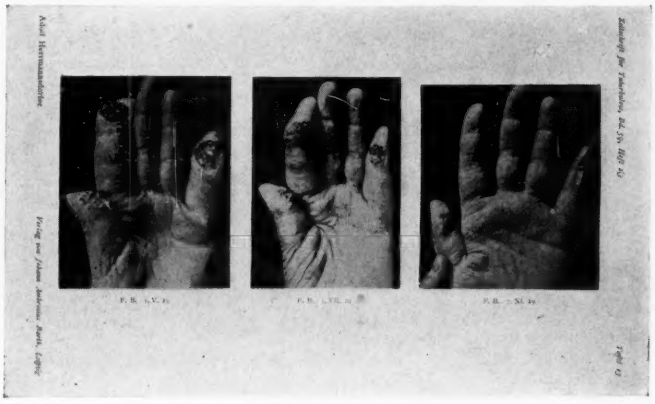


FIG. 16. Tuberculosis of soft parts of fingers. Healing with special dietary under controlled conditions.

paedics in the joint involved with bony destruction; why it should less commonly aid genitourinary tuberculosis and should prove of no real value in pulmonary tuberculosis,—all these and many other problems will find their solution only when the factors of dosage, time, immunobiology, pathological anatomy, and finally of the entire subject of the soil and its relation to the virulence of the organism have been more completely understood.

These problems bring to attention the need of revising our methods of evaluation of any therapy for all forms of tuberculosis in terms of these very factors mentioned. They also strongly point to a need of change of opinion of the effective therapeutic forces at play in the cure of some forms of extrapulmonary tuberculosis; thus, under treatment of the sun-

shine of even high-altitude resorts, they compel recognition in joint tuberculosis of the major rôle of orthopaedic immobilizing measures and of the secondary rôle of intense sunshine and moving air as agents of cure. Without a doubt it is to be admitted that light and fresh air favorably affect bodily physiology and the patient's psychology, but exact explanations of mode of action on the host as well as the definition of the effective spectral light regions cannot be clearly stated. With little hesitation we must also affirm that the intense highland sunshine can be most efficiently substituted by that of many lowlands or even by artificial-light sources. It is to be admitted in a similar manner that specific factors in climatic therapy must yet be demonstrated, but that the claims of the old health-resorts for the treatment of tuberculosis must rest to-day chiefly upon educational gains, advantages of group curing and other social factors.

Current contributions to nutritional therapy, as well as to the study of light, are truly leading to a better understanding of their biological action, and observations have been slowly developing a scientific background. The correlation of vitamine production with light energy—the possible formation of vitamine C from the ultraviolet irradiation of narcotin derivatives which are present abundantly in unripe fruits, whereas the antiscorbutic vitamine is so rich in the juices of ripe fruits;[3] the association of vitamine A with the chlorophyll of plants, and the provitamine-A factor, carotin in green cabbage, lettuce and asparagus and its deficiency in the bleached vegetables and in etiolated plants, dried seeds and in mushrooms that thrive in darkness; the true production of vitamine-D factor by specific bands of the ultraviolet are all emphasizing the possible importance that these two related therapeutic factors may have upon our bodily economy both in health and in disease.

The effect of the lack of vitamine-C and D intake in the production of experimental intestinal tuberculosis in animals fed tuberculous sputum is strongly suggested by reports of Smith and McConky. The clinical evidence of the favorable effect on symptoms obtained by feeding a rich vitamine diet in this form of disease by McConky and others is somewhat corroborative. Disturbance in the balance of vitamine supply can be shown to affect, favorably or unfavorably, the development of this form of tuberculosis in animals. However, correlation of vitamine-C and D intake with changes in the absorption of calcium from the intestines in

[3] Vitamine C is now more closely associated with hexuronic acid.

tuberculosis is still too speculative, although the utilization of bone salts in times of stress has been clearly shown to be favored by an abundance of vitamine C.

Studies with monochromatic radiation of the absorption spectra of components of cellular structure, the lipoid and protein fractions (even

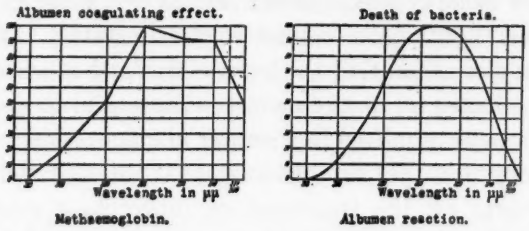


FIG. 17. Ultraviolet region of 265mμ that selectively affects protein and certain bacteria. (Colon bacillus and staphylococcus.)

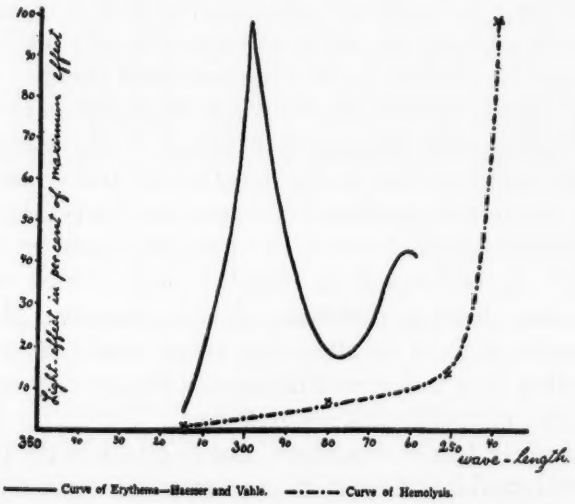


FIG. 18. Graph showing ultraviolet regions, 320–297 mμ and 260 mμ, that produce erythema and the region that has apparent selective affinity for lipoid (250 mμ).

to nuclear absorption) of the effect of bands of light on single cells and bacteria, on ferments and viruses, on cellular nutrition, are all tending toward more exact knowledge of specificity of action for certain frequencies of light-waves, and so toward a better evaluation of the effect of this therapeutic agent upon the soil of the tuberculous host.

CONCLUSION

In conclusion, the effectiveness of these preventive and therapeutic measures is shown by the statistical reports indicating the great decrease in tuberculosis mortality in the past 30 years. Since 1900, figures in the United States show a lowering of mortality, from 195.2 per 100,000 to 67.2 per 100,000 in 1930, and it is estimated that by 1937 the level of 40 per 100,000 will be reached in certain of the Northeastern states, unless the world-wide economic depression will interfere. However, the figures for the morbidity rate still remain at a high level, but are difficult of interpretation because of the constant improvement in means of early diagnosis and so forth. The rate of decline in mortality in middle- and old-age groups and in young male adults has continued, but the peak of mortality still remains in the group of young adult women. However, between the ages of fifteen and thirty-five years tuberculosis still remains among the chief causes of death.

Along with the advanced therapeutic measures of the past decade, a singular change has taken place in our methods of diagnosing the onset of tuberculosis and of following its course. The importance of consecutive X-ray examinations for study of the development of changes of the clinical-pathological lesion in the lung, and discovery of deep-seated areas of the disease and of localized atelectasis not detectable by physical examination but revealed so clearly by X-ray have been recognized; demonstration of cavities which would otherwise be too small to detect or whose pathological nature is such as to render them inaudible; of the early infiltrate in the infraclavicular region, which is so rarely detectable by physical examination:—such studies were indeed bound to influence our methods of treatment.

As has been so well stressed by Fischel, measures of therapeusis in the past have been focused upon long periods of healing, during which the patient has had to recuperate from the after-effects of acute reactivations and disseminations of his disease. Having learned from this to direct immediate attention to treatment during the period when added activity and extension of the disease are threatening, should we not improve our results?

We now recognize through newly accepted blood indices (as well as through other measures) that clinical recovery may exist while pathological activity is still present; that patent cavities remain a menace; and that rigid cavities are as a rule not compatible with a long survival

of the patient, and perhaps that means of preventing their formation are present. We now realize, too, the great importance of the factor of time, and we know that indications may be valuable only for the brief period of the particular stage of the disease. It is evident that the ominous significance of cavities increases in proportion to the nature and extent of surrounding disease, to their number and dimensions and perhaps location, as well as to their age. Changes in their development can occur with perplexing speed, so that opportunities for conservative interference can be swiftly lost, and more radical measures be indicated. It may be that in the history of every patient there was a time, even of short duration, when some method of collapse was indicated and would have favorably influenced the disease. Recognition of all of these factors together with the need of a uniform method of classifying patients on the basis of their pulmonary lesions in order to arrive at a rational standardization in choosing patients for the proper application of surgical measures should indicate that the future points to a greater number of economic recoveries. Until this is done, the comparison of results in various clinics will remain difficult of interpretation.

One may predict this and yet acknowledge conservatively that the use of pneumothorax, of phrenic-nerve operations, of thoracoplasty and similar procedures have had a combined successful effect in bringing economic recovery to about 20 per cent of otherwise apparently hopeless cases.

We have also for our use an advancing knowledge of dietary and vitamine studies in relation to mineral economy and a wider knowledge of biochemistry and of the physiological effects of light and air in their relation to the maintenance of health. These, when correlated in time with better understood states of immunity and hypersensitiveness and with a more exact definition of infecting dosage, virulence of the bacilli and tuberculosis pathology, may point to an added approach for the more complete attainment of attack on the bacillus, an approach through a change in the soil of the host, rather than through an attack on the parasite.

SPONTANEOUS PNEUMOTHORAX WITH AORTIC ANEURYSM AND PULMONARY FIBROSIS[1]

CLARENCE H. KETTERER

The following case is presented not only because of the rarity of the combination of findings but also because of the diagnostic difficulties encountered.

A colored male laborer, aged about 50 years, came to the cardiac clinic of the Western Pennsylvania Hospital complaining of increasing shortness of breath for the past three months. This was gradual in onset, with no history of sudden severe pain in the chest. He also complained of "bronchial trouble," manifest by slight cough, some expectoration, and "wheezing in the throat." These complaints were emphasized on exertion, with a sensation of laryngeal obstruction.

He had worked for ten years as a stoker in a gas-manufacturing plant using soft coal, and frequently was unable to see across the room on account of the smoke and dust. Following this, he worked as a laborer, loading and unloading brick. His wife had four still-births before the birth of a daughter now 18 years old. There have been no pregnancies since. At the age of 21 he had a chancre. While he was subject to frequent colds, no positive data could be obtained after careful questioning regarding symptoms and exposure to tuberculosis.

The chest on inspection appeared of normal size and shape. The ribs were prominent, the clavicles projecting slightly with a moderate falling in of the tissues above and below. No deformities, prominences, or increase in the size of the chest were noted. Mobility was greatly restricted on the left side. The cardiac impulse could not be seen, but could be heard best in the fourth interspace about 3 cm. from the midsternal line and to the right. The heart could not be outlined nor could retromanubrial dulness be made out.

Vocal fremitus was diminished on the left side. Tympanitic resonance was present throughout the lungs, with hyperresonance on the left. Breath-sounds were quite feeble and distant at the left base, while expiration was prolonged with loud vesicular breathing over the right base. From the first to the fifth dorsal spine whispered voice on the right was increased with occasional crepitant râles.

[1] From the Cardiac Clinic, Western Pennsylvania Hospital, Pittsburgh, Pennsylvania.

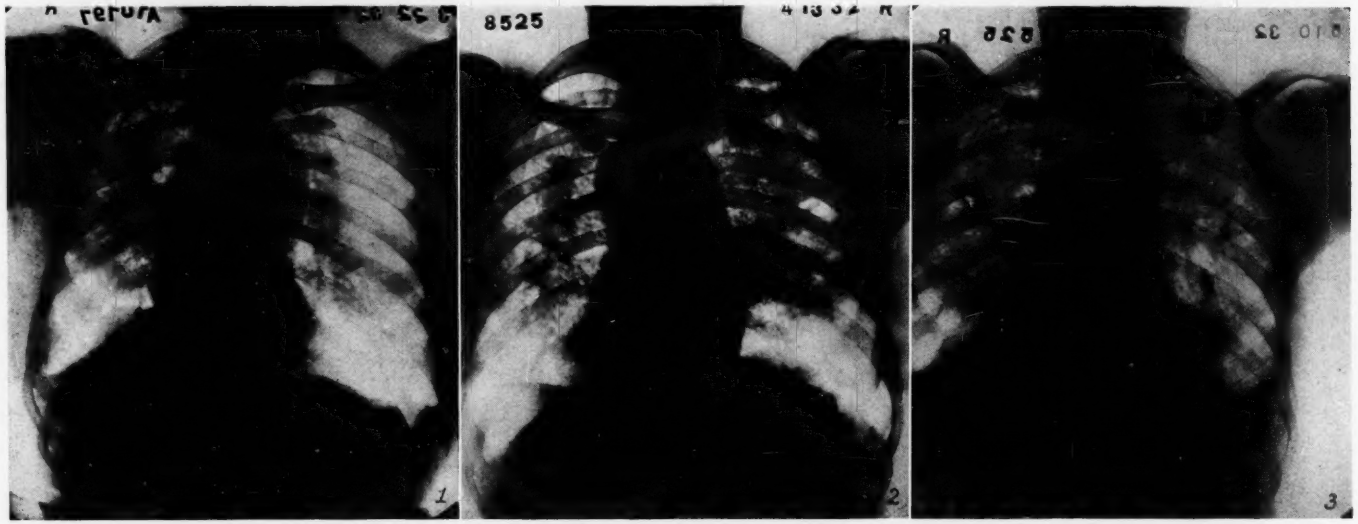


FIG. 1 FIG. 2 FIG. 3

FIG. 1. SHOWING ANEURYSM WITH PARTIAL PNEUMOTHORAX ON LEFT AND A GREAT DEAL OF FIBROSIS THROUGHOUT RIGHT
FIG. 2. INCREASED EXPANSION ON LEFT AND MORE PNEUMOTHORAX ON RIGHT
FIG. 3. APPEARANCE OF CHEST AFTER FIVE MONTHS' ANTISYPHILITIC TREATMENT

Fluoroscopic examination was as follows:

The heart is normal in size but the aorta is increased in width both to the left and right. There is nodular enlargement on the inner side of the right diaphragm which suggests pathology in the liver. There are adhesions at both bases. There is a partial pneumothorax on the left side with compression of the upper lobe. There is retraction of the right apex with a great deal of fibrosis through this entire lobe. The lung changes may be entirely due to tuberculosis, pneumonoconiosis or lues.

Eight sputum examinations were negative for acid-fast bacilli. Three Kahn tests were negative, one after the patient had been given 0.6 gm. neoarsphenamine. The spinal fluid was also negative. The electrocardiogram showed a sinus tachycardia with ectopic beats of multiple origin. The *P* wave was of variable contour, frequently notched. The *R* wave had a low and variable potential in all leads.

In this case the pneumothorax occurred insidiously, for there was no history of sudden sharp pain with general symptoms of collapse. The only complaint was shortness of breath, which in the past three months had become worse, especially on exercise. The leakage therefore was slow, symptoms being absent because of the adjustment of respiration and circulation to the gradual accumulation of air. A pneumothorax occurring so insidiously that its presence is unsuspected until revealed by physical examination is particularly true in patients with pulmonary tuberculosis.

Spontaneous pneumothorax is a rather frequent accident in silicosis and usually the partial lung collapse is seen in the upper-chest or upper-lobe region, probably where adhesions are not so pronounced. Pneumonoconiosis, as a possible aetiological factor, must be considered, since there is a history of inhalation of inorganic dusts sufficient to account for the fibroid nature of the lung changes. We must bear in mind that a short-time exposure in one who has signs of extensive pulmonary disease is in all likelihood not pneumonoconiosis. While myocardial insufficiency may be a terminal event in advanced pneumonoconiosis and responsible also for a similar picture, there was no history or clinical evidence of congestive failure.

Pancoast and Pendergrass mention the possible combined effects of passive congestion from cardiac decompensation and silicosis. In the presence of frank decompensation the accompanying passive congestion would seem to intensify the appearance of any of the stage of silicosis. In the so-called first stage of silicosis the appearance of both conditions is very much the same and may be almost or quite indistinguishable.

When tuberculosis is superimposed, there are added the general symptoms of fever, rapid pulse, sweats, weakness, and emaciation, although in some patients constitutional symptoms are relatively slight, due to a nontoxic form of the disease. This patient had an infrequent cough, with occasional expectoration of blackish substance and with subjective sensations of "gurgling" in his chest but at no time was the cough severe or associated with mucopurulent expectoration. The only significant thing was the shortness of breath on slight exertion with occasional wheezing, but he was not distressed while resting and there was entire absence of pain.

The similarity of signs of pneumonoconiosis and advanced tuberculosis and the frequent association of the two diseases render exclusion of tuberculosis impossible without a clear knowledge of the history and careful and repeated sputum examinations. Landis states that "changes are not due to the dust itself but to the fibrosis which the dust causes."

It is uncertain just how much the appearance of silicosis may be simulated by coincident syphilis of the lung. The incidence of pulmonary syphilis is denied by many and the roentgenologist is rather loath to make a diagnosis of syphilitic pulmonary lesions. It is inferred that every silicotic individual with a positive Wassermann reaction must await the results of treatment before a final decision is reached as to the degree and extent of the silicosis.

Accurate information concerning the frequency of acquired pulmonary syphilis is not available. Gummata of the lung may be latent. They have been found at autopsy in those who during life gave no evidence of pulmonary disease. Syphilis of the lung may manifest itself as a local or diffuse fibrosis, but such a lesion seldom possesses characteristics sufficient to distinguish it from fibrosis due to other causes.

It has been said that we shall find more cases of pulmonary syphilis than we have in the past in direct proportion to the care with which we study patients with supposedly unquestioned pulmonary tuberculosis. This condition is so common that many physicians are content with the diagnosis, once it has been made, especially if the signs and symptoms suggest advanced disease. Repeatedly negative sputum examinations may fail to suggest that the diagnosis should be reconsidered, and a roentgen-ray examination has not been made or has been wrongly interpreted as the picture may resemble tuberculosis.

A positive Wassermann does not mean that a pulmonary lesion is of necessity syphilitic. Tuberculosis and syphilis may frequently coexist. The Wassermann reaction becomes diagnostically important in regard to

a pulmonary lesion when all tests for tuberculosis are negative. Negative Wassermann reactions may be found in cases of aneurysm which give historical or other anatomical evidence of syphilis. McCallum in his *Text Book of Pathology* is convinced that all are due to syphilis. Tyler states that "the percentage of aneurism in nonsyphilitic patients is so small that it is almost negligible."

According to Jores, tuberculosis may lead to erosion aneurysm, especially of the larger arteries. The walls of such aneurysms are not infrequently formed of granulation tissue or of caseous matter into which thrombotic masses progressively deposit. Also, in the vascular wall itself tuberculosis may be demonstrated. Tuberculous aneurysms may be due to caseated mediastinal lymph nodes, and it is evident that pulmonary tuberculosis is sometimes associated with aneurysm.

Hanan and Sieg describe a case of rupture of an aortic aneurysm into a tuberculous pulmonary cavity, in which the entire aortic wall, and especially about the site of the aneurysm, was formed or infiltrated by caseotuberculous tissue. Edenhuisen describes a case of perforation of the descending aorta into the oesophagus with the simultaneous indurating chronic tuberculosis. At the upper margin of the perforation of the aorta, a caseous nodule was found. Also, the margins of the oesophageal perforation contained, microscopically, demonstrable tuberculous tissue. The external wall of the aorta showed tuberculous granulation tissue also.

Pel reports a case of aortic aneurysm in a patient with pulmonary tuberculosis. In discussing this case, DeCosta suggested that the aortic condition was due to syphilis and the tuberculosis secondary, referring to the exacerbating effect of syphilis upon tuberculosis and *vice versa*.

SUMMARY

1. While the X-ray findings in the above case suggest pulmonary tuberculosis, this was ruled out clinically and by laboratory tests.

2. The history, together with X-ray findings of aneurysm, is indicative of syphilis.

3. The therapeutic test failed to have any appreciable effect on the pulmonary fibrosis after five months of antisyphilitic treatment. One cannot at this time, however, insist that the fibrosis is not of syphilitic origin.

4. The history of the prolonged exposure to coal dust, together with the fact that pneumothorax is a rather frequent accident in these cases

and with the other aetiological factors eliminated, we are led to believe that the aneurysm in this case was incidental and that the pneumothorax was caused by the pneumonoconiosis, in the absence of demonstrable tuberculosis and the persistence of the fibrosis following intensive antisyphilitic treatment.

REFERENCES

(1) Funk, E. H.: Chronic diseases of the respiratory tract., Oxford Monographs, v, pp. 260, 261, 272, 273, 278.
(2) Pancoast, H. K., and Pendergrass, E. F.: Amer. Jour. Roentgenol. & Radium Ther., 1931, no. 4, 568.
(3) Landis, H. R. M.: Pneumoconiosis, Osler's Modern Medicine, Philadelphia, 1927, iv, 211.
(4) Adams, L. J.: Tuberculosis of the aorta, Arch. Int. Med., 1929, xliv, 711.
(5) U. S. Public Health Bulletin No. 187: The health of workers in dusty trades.
(6) Aortic aneurism with spontaneous pneumothorax: Report of a case, Ohio State J. Med., 1923, xix, 397.
(7) Tuberculosis of the large arteries, Jour. Am. Med. Ass., 1913, lv, 1413.
(8) Palasse and Cade: Aortic aneurism with pulmonary tuberculosis and pleural effusion, Lyon Med., 1929, cxliii, 297.

STUDIES ON THE PATHOGENESIS OF PRIMARY TUBERCULOUS INFECTION[1,2]

I. THE REGRESSIVE LESIONS

HENRY C. SWEANY

The pathological anatomy of primary tuberculous infection would be of little moment without a knowledge of the mechanism of the various processes that enter into the changes. It is my purpose in this paper to attempt to elucidate one phase of this subject, which we may designate the most extreme retrogressive tuberculous process, and which embraces the phenomena of calcification, ossification, and resorption of the primary lesion. Although this information may not be all new or of immediate practical application, there are several new facts that will be of interest to present. Because of the nature of this work it aptly may be called the "archaeology" of tuberculosis. From these extinct remnants we are able to reconstruct the type of activity that once went on in the buried terrain of tubercle bacilli, but, like the ancient sites of the human race, was either entirely destroyed or only a few stragglers migrated to other parts to start all over again. Sometimes they went just outside of the city walls to rebuild; sometimes they surrounded the older structures or built on top of them, while most of the time they went beyond the pale entirely. In this one respect we may compare the tubercle bacilli to men.

The subject of calcification is a very old one, but the mechanism of its deposition is not entirely understood, and this is what we are concerned with here. Schürmann (1) has given an excellent review of the history of calcifications in tuberculous lesions. Küss (2), however, gave the first clear picture of calcification and petrifaction of the primary tuberculous lesions, both local lesions and those situated in the lymph nodes. Then came E. Albrecht (3), H. Albrecht (4), Ghon (5) and Ranke (6), whose various contributions take first rank in the study of these retrogressive lesions. It may be said without risk of error that the work of

[1] From the Research Laboratories of the Chicago Municipal Tuberculosis Sanitarium, Chicago, Illinois.

[2] Read in part at the twenty-eighth annual meeting of the National Tuberculosis Association, Colorado Springs, Colorado, June 6–9, 1932.

these pioneers established the fact that a retrogressive tuberculous lesion of any significant size *must undergo encapsulation, calcification and petrifaction* in the due process of healing. It is as much a law as Parrot's *adenopathies similaires* or the Cornet-Cohnheim law. Just as nature attempts to wall off necrosis and caseation by the various *échelons* of body-cells, so, after this encapsulation has been effected, does she carry on further by a liquefaction of *caseum*, a deposition of lime salts, a lysis of fibrous tissue, a laying-down of bone, a resorption of the fibrous tissue and calcific deposits, and, finally, an attempt at resorption of the bone itself with a replacement by a vascular stroma resembling sometimes lymphoid and sometimes marrow tissue.

Although Küss, Ghon, and other early workers spoke of "petrifaction," it was Beusen (7), Pollack (8), and Puhl (9) who deserve great credit for the development of the knowledge concerning the formation of bone in the tuberculous focus. In the course of calcification the inner layers of the "specific capsule" were found gradually to become transformed into cells that resembled bone. Inasmuch as no true bone-cells could be found in that vicinity, nor could any migration of bone-cells be accounted for, it was correctly assumed to be due to a gradual transformation of the fibrous tissue by indirect metaplasia (Ribbert) into bone-cells. Jaffé and Levinson (10) describe the process as a loosening and cell-proliferation of the specific capsule; an increase of the fibrocytes and histiocytes between the hyaline trabeculae; a replacement of the hyaline membrane by a pale-stained substance; and the appearance near a calcified centre of an oxyphilic band that encloses the fibrocytes which then take on the appearance of preosseous tissue. Both Puhl (11) and Simon (12) have reported bone-formation in calcifications of tuberculous reinfections that underwent healing with ossification, although less frequently. Therefore, just as calcification is a process of degeneration preceding regeneration, so ossification is one of regeneration of calcified foci that frequently accompanies the process of resorption; although many times it is a late development, and, as the succeeding work seems to show, only indicative of healing under favorable conditions.

METHOD OF STUDY

Radiographs were obtained before the necropsy, if a recent picture were not available. Then the lungs were removed as carefully as possible and inflated to approximately the same size of the chest. Usually the latter was a little larger than average, because the postmortem chest represents conditions on

expiration. Our aim was to obtain an average-sized and not an over-distended lung. After placing suitable markings for identification and to indicate the shift, stereoexposures were made, using low voltage and amperage and a long time-interval. This brought out detail in a manner not possible by the antemortem technique, and allowed us to locate calcifications as small as a millimetre in diameter,—a thing not possible by any practical section method. After hardening the specimen, thin sections were made from the anterior to the posterior part by means of a large knife, and the calcifications (and other lesions) searched for, after being located by the radiographs. Rarely did we have to resort to the stereo-films to find the object, and only very few were missed that we set out to find.

THE MATERIAL USED

The material consisted of 183 lung specimens from our hospital, together with five "normal" lung specimens from the Cook County Hospital, all of which had calcified foci of various ages and sizes. Of the 183 specimens, 36 contained such large cavities in the same lobe of the lesions under study that any localizations were impossible. So these were eliminated from that group, although some were used in studying the type of hilum or lymph-node lesion. There were 22 more recent primary lesions, six of which were of the "adult type." These specimens are not included in this study, because the primary purpose of this work is to study the older lesions, beginning with the first signs of calcification and following them on through their various changes, which first are degenerative and then reparative.

THE INCIDENCE AND POSITION OF CALCIFIED AND OSSIFIED PRIMARY LESIONS LOCATED BY ROENTGENOGRAM AND SECTION

The old calcified foci were selected from 129 pairs of lungs, about which the location of the lesions could be ascertained with a reasonable degree of accuracy. Of these, 53 primary lesions were found in both the lung parenchyma and lymph nodes; 12 were found only in the lymph nodes; 23 only in the parenchyma; 11 were atypical (perhaps calcifications from reinfections); while 30 had no calcifications that would cast a shadow on the postmortem X-ray plate. This means that they could not be found by macroscopic search, if present at all.

We were reasonably certain that there were calcified primary lesions in 88 specimens, 76 of which were in the parenchyma and 65 in the lymph nodes. Of this group, 47 were single, 17 double, 9 triple, 22 four or more, and one having more than 15 separate foci. Of the first three groups (single, double and triple lesions), the right upper had 21, the middle 2,

the right lower 30; while the left upper had 19 and the left lower 32, most of which were situated beneath the pleura or along the lobe margins. Many times they were found in two or more lobes and several times in both lungs. There were 42 in the upper and middle and 62 in the lower lobes. These observations seem to coincide more with the work of Küss than Ghon, in respect to the lobar distribution. The former found more in the lower lobes than in the upper, while Ghon's figures show 61.27 per cent in the upper (including middle) and 38.73 per cent in the lower, although both report rare findings in the apex. Ghon found more in the anterior part of the upper lobes and the posterior parts of the lower, with most involvements not far beneath the pleura. Practically all agree that the localizations occur in the most-used parts of the lungs; that is, in direct ratio to the aerogenous contact. Although it does appear like an aerogenous process, there are some features yet to be explained, especially when there are multiple localizations. In one specimen of this series there were more than 15 typical parenchymal lesions scattered over both lungs. Such a localization resembles either a haematogenous dissemination or a peculiar bronchogenic spread after the bacilli landed from without. I am not sure that the latter may not be possible with a small number of strains of tubercle bacilli that begin by a rapid multiplication and gradually resume their slow development as they meet with resistance in the host. Lurie (13) has shown that lung tissue is a good medium for the growth of tubercle bacilli.

INCIDENCE OF OSSIFICATION IN TUBERCULOUS LUNG LESIONS

In a search for the presence of bone in the primary lesions, 132 pairs of lungs were studied and decalcifications made on the parenchymal and lymph-node lesions. Sections were made at various levels and stained for fibrous and elastic tissue as well as the routine haematoxylin and eosin. If the first findings were negative, new sections were cut until the desired results were obtained. In the parenchymal lesions there were 84 calcifications of varying degrees of hardness, with 22 showing bone; and 97 calcifications of lymph nodes, with 23 showing bone. Only 25.1 per cent of these calcified lesions, therefore, revealed the presence of bone. About equally divided between parenchyma and lymph nodes, the presence of bone seems to depend on the size and degree of encapsulation of the lesion and not the location. Although serial sections may have revealed a few more, it is a general rule to find the bone well distributed when

present at all. This is lower than Puhl's figures of 50 per cent for primary and 7 per cent for secondary lesions. I can't help but feel that the type of material accounts for this difference.

The presence of bone was more common in the completely healed foci than in calcified lesions associated in advanced tuberculosis, even though it were primary in character. This would seem to indicate that bone-formation is a favorable sign and may be looked upon as one of the healing factors under favorable conditions, even though it may not be a common or important one.

MISCELLANEOUS OBSERVATIONS

Of 98 definite calcifications on the postmortem film, only 48 could be definitely seen by antemortem radiograph, a fact that will be of interest and value to roentgenologists.

One of the most interesting groups was one of 10 cases in which the old primary focus was very small and was in what appeared to be a process of complete resorption. Many of these cases revealed a very acute type of tuberculosis of the "juvenile" or "adolescent" type, while some were simply acute tuberculosis of the secondary type. All but one was under 23 years of age.

Of 30 showing no calcifications, a few were fibroid where the old lesions may have been resorbed, a few were only acute tuberculosis where the primary focus may have been too small to leave a residue, while a few were "juvenile" and not unlike the group just preceding, in which definite calcified lesions were found. It suggests that there had been some factor that had previously altered the tuberculous reaction without leaving any trace, because none of these were entirely like a primary reaction, yet many were extremely acute.

Finally, there were 6 cases in which we could find little if any trace of a former infection; in fact, in which it was most probably lacking. In these the local reaction resembled that of a primary focus, but the lymphatic reaction was mild or entirely absent, except for cellular hypertrophy in the lymph-sinuses, with an occasional small tubercle or giant cell. Of the permanent calcified lesions mentioned before, there were more in the parenchyma than in the lymph nodes, showing that a difference exists even in the average run of tuberculosis. The difference is so great and the characteristics so marked that we are of the opinion that the lymph-node reaction tends to become less in adults, everything else being equal. This observation has been reported by Blumenberg (14), who rejects the

Ranke theory on this ground. This group, however, will be studied more in detail in a subsequent work.

A STUDY OF THE MECHANISM OF CALCIFICATION

With regard to the problem of calcification, it is evident that it begins to take place in any closed caseous focus a very short time after caseation. One patient, 5 months and 19 days old, began to show deposits of calcium, while two others, about a year old, had large amounts of calcium. This confirms the findings of Küss, Gerpel, and others. It is not necessarily a matter of age or of waiting for something favorable or unfavorable to happen, but in general a matter of chemical equilibrium between the autolyzing *caseum*, containing acids of sulphur and carbonic acid, and the calcium from the blood that is gradually infused into the *caseum*. We are not sure, however, that age, diet, etc., may not have a minor influence.

A very interesting phase of this mechanism is the periodic precipitation of the calcium. Not uncommonly, in fact frequently, the deposition of calcium takes place in periodic waves resembling and perhaps identical with the periodic precipitation known as the "Liesegang phenomenon." This is well illustrated by Pagel (15), and Jaffé and Levinson (10). The first signs of calcific deposit in fresh tubercles usually shows somewhere in the centre of the caseous mass. As the lesion ages and perhaps the enzyme action that precedes the precipitation of calcium reaches toward the periphery, ring upon ring will appear until the specific capsule is reached. Here the autolytic process seems to continue, and, as the lesion gets older, one of two phenomena appear, namely, either a calcification and resorption of the inner layer of the capsule takes place, or a protrusion of the fibrocytes of the inner layer toward the centre of the mass (see plate 1). Sometimes both occur simultaneously. The former seems to follow in the wake of the calcification that has spread outward from the centre and has continued into the capsule itself. The latter seems to arise from a part of the capsule still containing nourishment from the capillaries, and is able, therefore, to proliferate toward the centre, carrying in strands of fibrous tissue that subsequently help to break up the mass of calcified caseous material for ultimate resorption. The former is, therefore, degenerative; the latter regenerative. This process has been shown by Huebschmann (16), Mebius (17), Pagel (15) and others.

In interpreting this process we must bear in mind that the primary is fundamentally different from later lesions. The first mass of tissue that is enclosed has not been subjected to the same action that is met with by

secondary tubercles. The allergy that develops later has not had an opportunity to exert its effect upon these cells. So, while they become caseated and apparently destroyed, appropriate stains, as pointed out by Ranke (6), will show that the cellular framework is still intact and the elastic fibres are the last to be destroyed. They may be found even in old calcified and ossified tubercles. This partially destroyed tissue, therefore, undoubtedly undergoes gradual lysis from autolytic ferments from within or from enzymes gradually infused from without, and the process of completing the lysis continues. Under the high-power microscope, the clearing appears first in small foci,—too small to show resolution with any magnification, and gradually enlarging until they appear like little globules having clear centres and a dark deposit around the outside, and finally becoming large and irregular and developing heavy walls, producing a honey-combed effect. The former constituents of the tissue and the caseous material have been autolyzed in these tiny foci, and the acids remaining unite with the calcium to produce a precipitate of calcium sulphate and other salts that take the alkaline stains (haematoxylin). The process may be compared to a slow setting of mortar or plaster-of-paris, because both reactions may be theoretically derived from the ingredients present.

As pointed out before, the process does not always stop when it reaches the wall of the capsule, but sometimes it continues on into the heavy hyalinized wall in the same manner it did in the caseous material. Small foci appear, that gradually enlarge until they finally coalesce and produce deep erosions in the hyaline wall, leaving only globules of calcium. This process may proceed until the entire wall is eroded away, but this does not occur equally at all places.

THE PROCESS OF OSSIFICATION

In some places the inner layer may suddenly develop fibroösteoid tissue that first stains a dense pink, and then red; and finally true bone-cells appear from the old nuclei of the hyaline tissue. It may assume in places the appearance of an Haversian system. These various changes are illustrated in plate 1.

Usually the bone develops where there is contact with capillaries situated in the outside of the capsule. If the hyaline fibrils are entirely dead, however, and there is no chance to replenish the cells from without, the autolysis will proceed without bone-formation. Of course this does not mean that bone-formation will always occur in the presence of capil-

laries. Many factors enter in that cannot be accounted for with our present knowledge. The problem of progressive disease seems to prevent bone-formation, and perhaps diet is another influential factor. As bone seems to be present more in small completely healed primary foci, irrespective of age, it would seem to be more like the last stage of the reparative process. The 25 cases in which bone was present were distributed as follows according to age: 5 in the second decade, 7 in the third, 5 in the fourth, 2 in the fifth, 2 in the sixth, and 4 in the seventh. It is, therefore, not a problem of age but one of stage of repair of the particular lesion.

THE MECHANISM OF RESORPTION

Now, turning to the purely resorptive phase of the primary lesion, we have a process that is clearly one of attempted removal of a foreign material. As pointed out before, fibrils of connective tissue many times

---

PLATE 1

FIG. 1. A cross-section of the calcified lymph-node complex of patient *D. S.*, M. T. S. no. 28,184, a 17-year-old girl dying of advanced pulmonary tuberculosis. Note the lacuna in the capsule at *a*, with a thin rim of bone around it and the clearing in the centre at *b* with a rim of bone. Note also the irregular erosion of the "specific" capsule. × 5⅔.

FIG. 2. Higher magnification of small rectangular area of fig. 1. Note areolar structure with capillaries and margins of bone. × 221.

---

form within the inner wall of the specific capsule and extend into the mass of calcified caseous material in the centre. Or they may erode the inner layer of the specific capsule itself, leaving lacunae, around the walls of which fibroösteoid tissue forms, followed by the appearance of true bone-cells (see plates 1 & 2). This is the manner usually described as being characteristic. It sometimes breaks the lesion up into numerous islands. The fibrous tissue appears to resorb the calcified mass as it grows into it, and to use the liberated calcium to form new bone-tissue around the margin. At about this time centres of bone-formation may begin at various points along the inner margin of the newly formed lacunae, and extend along the margins of the connective-tissue bands. In some places the new bone extends directly into the calcified mass, resorbing calcium, and then extending outward, and at the same time resorption appears in the centre of the bony mass, leaving a myxomatoid tissue in its wake. Finally, only a thin shell of bone remains, with a network of capillaries containing newly formed tissue resembling bone-marrow, but with-

Fig. 1

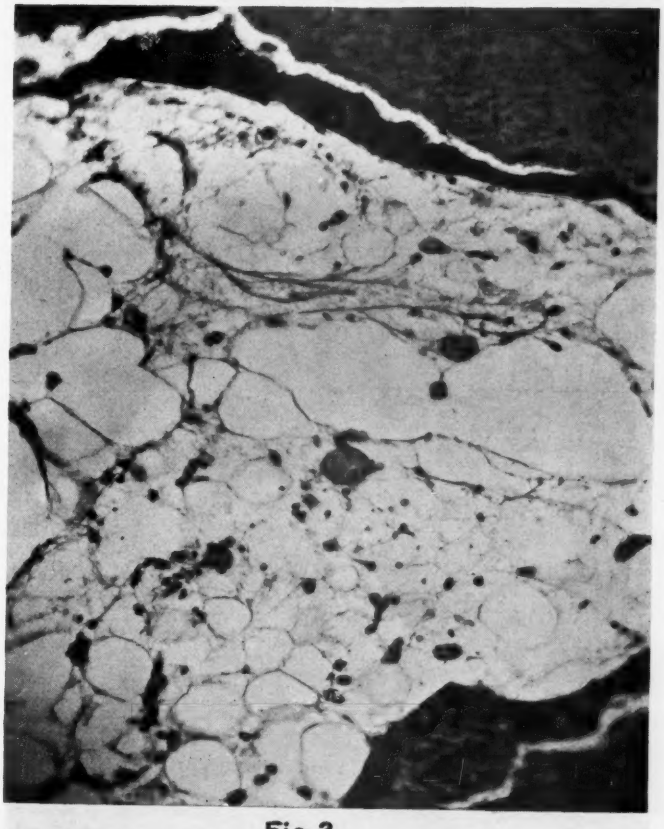


Fig. 2

PLATE 1

out the rich cellular constituents of the latter. Usually there is only a thin myxomatous stroma containing blood-vessels, but occasionally lymphoid cells could be found and in other places plasma cells and myelocytes, but no giant cells or erythroblasts. Mebius (17) reported one instance of the presence of red marrow.

In certain old lesions there may be only a small spicule of bone left in a completely regenerated lesion, indicating that the process proceeds toward a complete resorption and that the absence alone of calcified lesions does not prove the absence of an older infection. On the other hand, we must not overlook the possibility nowadays of reaching adult life without any tuberculous infection at all.

THE RELATION OF REABSORPTION TO REINFECTION

There was one aspect of this problem on which we were unable to throw any light; that is, whether the destruction of the walls of these old tubercles may not lead to a liberation of the latent bacilli. Judging from the

---

PLATE 2

FIG. 1. Postmortem radiograph of lung of patient *R. O.*, M. T. S. no. 28,365, age 22 years, revealing a far-advanced pulmonary tuberculosis with a healed primary complex.

FIG. 2. Microscopic photograph of a cross section of healed parenchymal tubercle indicated by arrow in fig. 1. Note the faint "Liesegang rings," the incutting of the capsule, and the clearing of central calcification with replacement by a marrow-like substance and bone-formation. × 13.5.

---

presence of live bacilli obtained from calcified and ossified foci, it is entirely possible that nature may defeat her own purpose in the resorption of the walls of the old tubercles. We found no evidence of recent infection around such foci that could not be accounted for by imagining a superinfection to have taken place. In a careful study of 5 "normal" lungs of young adults, four had living bacilli that we were able to grow on culture medium, while one (see plate 4) was sterile. There is no doubt that tubercle bacilli survive for a long time in old tuberculous lesions. It would be impossible to place a time-limit on this survival, as individual differences alter the circumstances. Opie and Aronson (18) have contributed some of our most valuable information on this subject. They report that the survival of tubercle bacilli in calcified lesions is about 20 per cent in a series of 169 autopsies in subjects in the later half of life. Many of these were due to reinfection, and the authors felt that most bacilli were

Fig. 1

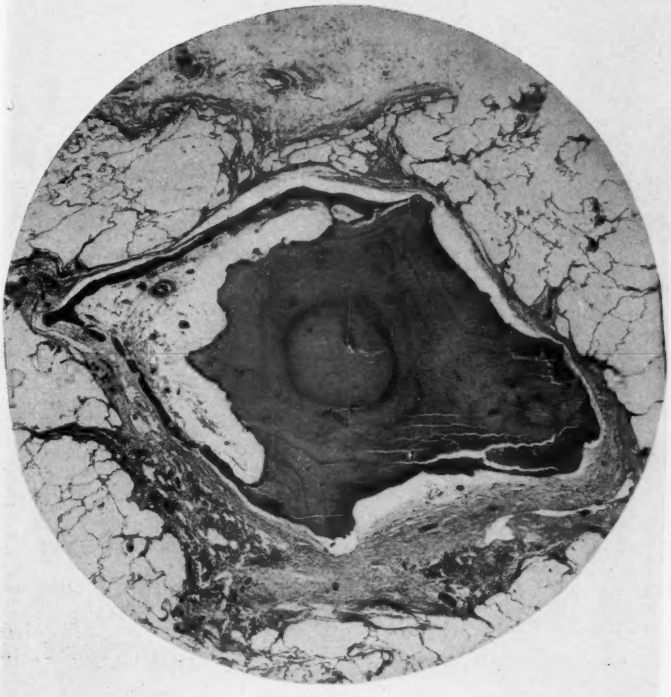


Fig. 2

PLATE 2

obtained from the pulmonic tissue and not the nodules. One case from which we grew tubercle bacilli is reproduced (see plate 3). This was of a young white female, dying in ectopic pregnancy, who appeared otherwise in perfect health. The tubercles in the lung were situated along the course of the left subapical bronchus. There were three or four local calcified accumulations and many small fibrous scars, indicating that the primary lesion had been a bronchopneumonia involving a large part of the lung supplied by the left subapical ramus. The largest local lesion, just below the pleura (figure 2, plate 3), revealed a well-formed specific capsule, without surrounding infiltration, giant cells or tubercles, but emphysema in the alveoli around and calcification within, but no bone. The first bronchial lymph nodes were about the same except there were one or two small centres of bone (figure 3, plate 3). The main bronchial lymph node contained living tubercle bacilli that grew on cream medium and produced many colonies, indicating that many living germs were

PLATE 3

FIG. 1. A postmortem radiograph of the left lung of a Cook County Hospital patient dying in ectopic pregnancy in young adult life. Note the multiple aspect of both the parenchymal as well as the lymph-node complex. The lesion at *1* is shown below in fig. 2 and the lesion at *2* is shown in fig. 3.

FIG. 2. A well-encapsulated local primary lesion. Note the so-called specific capsule with the beginning calcification of the inner layers (but no bone-formation) at *a*, the perifocal emphysema at *b*, and the fibrous cords leading toward the hilum at *c*. × 13.5.

FIG. 3. A small lymph-node lesion along the course of the lymphatics indicated in fig. 1 at *2*. Bone-formation has begun at *a*. Cultures of these lesions yielded abundant colonies of tubercle bacilli. × 13.5.

present. Although there was no sign of perifocal inflammation, it is easy to see how these lymph nodes could open up and allow the infection to become haematogenous through the capillary communication shown by Jaffé and Levinson, or permit it to extend to a neighboring lymph node and cause a smouldering infection that might break out any time. Such latent or occult forms are present in a large number of people but never reach the point of clinical disease. In this state of continued infection we have a secondary lymphatic type that continues from the primary focus and which has aptly been called by Bernard (19) "primary sequelae." Number 5, also from the Cook County Hospital was from a young negro dying of acute nonspecific peritonitis. There are the usual marks of the primary lesion present and the cream-medium culture was positive for

Fig. 1

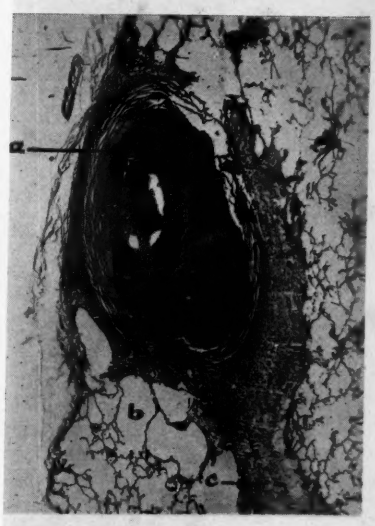


Fig. 2

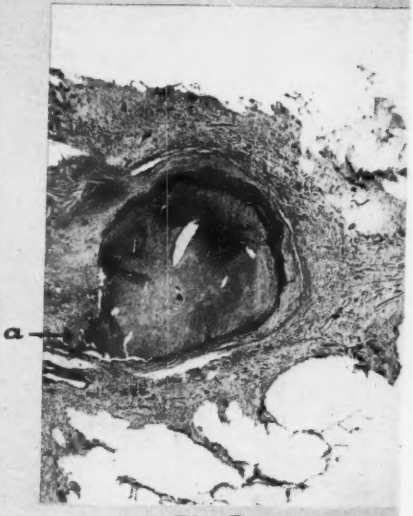


Fig. 3

PLATE 3

tubercle bacilli. Numbers 3 and 4 were also definite primary lesions in young adults dying of acute diseases in the Cook County Hospital. They had all the characteristics of primary lesions and also produced tubercle bacilli on culture. Number-2 culture, as stated above, was sterile.

This indicates that tubercle bacilli survive for at least 5 to 10 years in old foci, although according to Opie's findings we have no right to claim a much longer time. There is no doubt, however, that all these lesions extended back well into childhood. It does not mean, however, that a calcified and ossified lesion always requires ten years or more to form. The number-2 case was, in the first place, a very small lesion and there were no hilum-node metastases. It seemed to run its course in a short time and become sterile without metastasis or spread.

The average "healed" primary infection, however, may well account for a large number of reinfections because of the rare possibility of an individual living for ten or more years without a serious "health crisis" sufficient to unleash the dormant microörganisms.

PLATE 4

FIG. 1. A postmortem radiograph of the lung of a young man dying in the Cook County Hospital, of peritonitis. Only one small parenchymal calcified tubercle was present, as shown by the arrow.

FIG. 2. A microscopic photograph of tubercle shown in fig. 1. Note the bony ring with almost complete disappearance of capsule, and the extinct blood-vessels indicated at the arrows. Cultures of the node were sterile. × 56.

SUMMARY

A study of the regression of the primary tubercle has been made, based on the findings in 188 pairs of lungs removed at necropsy, radiographed, and sectioned by a special method. The incidence and location of these lesions were found in keeping with the ideas of Küss, Ghon and others, but there was a higher incidence of what appeared to be multiple primary residues. This was thought to be due to a more certain method of localization. Of 88 specimens of characteristic primary lesions 76 were in the parenchyma and 65 in the lymphatics. Twenty-three were located only in the parenchyma and 11 only in the lymph nodes.

In 84 calcified parenchymal lesions bone was found in 22; while in 97 lymph nodes bone was found in 23, revealing practically no difference in bone-formation between the local and lymphatic lesion and an incidence of 25.1 per cent of all without the usual lymph-node exaggeration. The

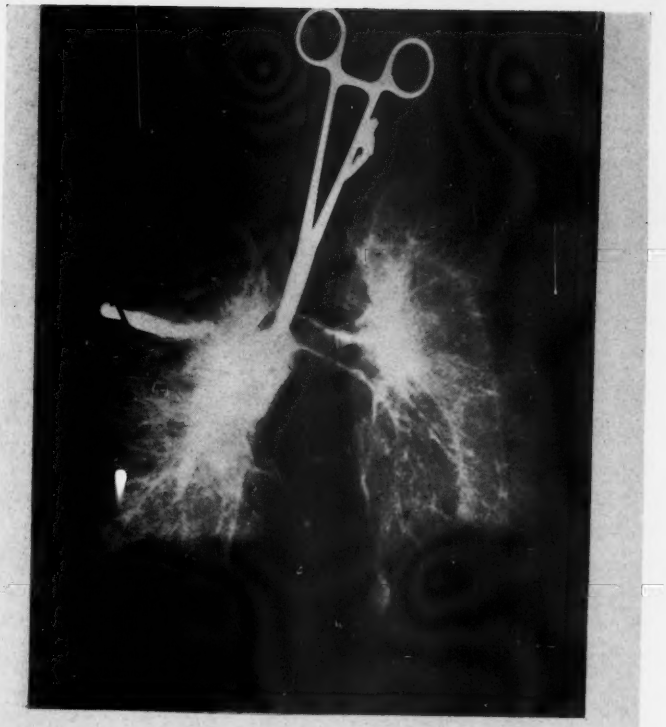


Fig. 1

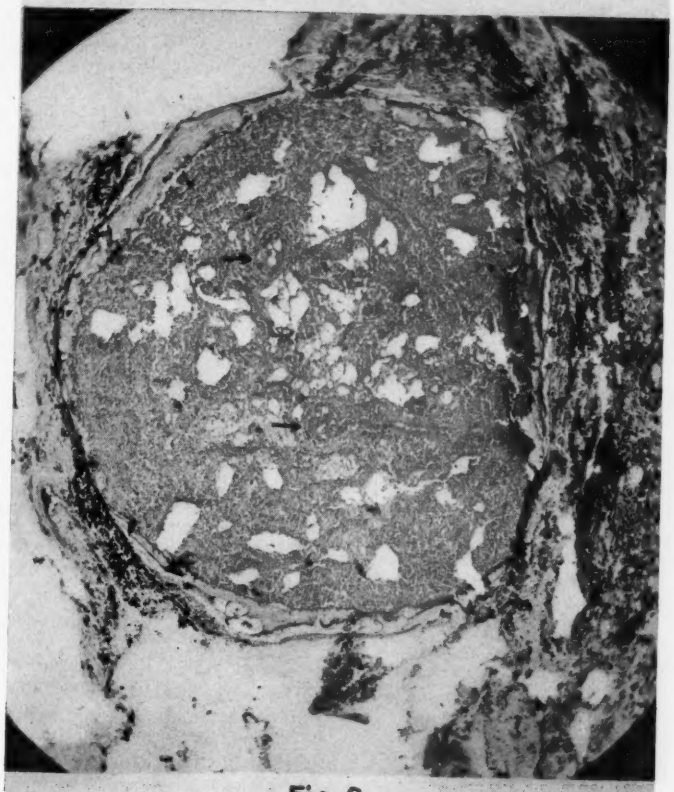


Fig. 2

mechanism of calcification, ossification and resorption are described. The question arose regarding the possibility of the liberation of tubercle bacilli as a result of the resorption of the walls of the primary lesion, because walls were entirely gone in more relatively young individuals (one 17 years old) while bacilli were living in most large primary lesions in people under 25 years of age.

Approximately half of the calcified parenchymal lesions may be seen on antemortem radiographs, for, out of 98 showing on the postmortem pictures, only 48 could be seen on the antemortem films. Ten contained very small primary lesions and thirty none at all. Many of these two groups showed a modified type of primary lesion, indicating that there had been only a partial sensitizing effect from the first infection. Six appeared to be adult primary lesions.

REFERENCES

(1) SCHÜRMANN, P.: Arch. f. Path., Anat. u. Physiol., 1928, cclxix, 355.
(2) KÜSS, G.: De l'hérédite parasitaire de la tuberculose humaine, Paris, 1898.
(3) ALBRECHT, E.: Frankfurt. Zeitschr. f. Path., 1907, i, 214.
(4) ALBRECHT, H.: Wien. klin. Wchnschr., 1909, xxii, 327.
(5) GHON, A.: Primary lung focus of tuberculosis in children, London, 1916.
(6) RANKE, K. E.: Ausgewählte Schriften zur Tuberkulosepathologie, Berlin, 1928.
(7) BEUSEN, W.: Inaugural dissertation, Göttingen, 1898.
(8) POLLACK, K.: Arch. f. Anat. u. Physiol., 1901, clxv, 129.
(9) PUHL, H.: Beitr. z. Klin. d. Tuberk., 1922, lii, 116.
(10) JAFFÉ, R. H., AND LEVINSON, S. A.: Amer. Rev. Tuberc., 1929, xx, 214.
(11) PUHL, H.: Beitr. z. Klin. d. Tuberk., 1922, lii, 116.
(12) SIMON, G.: Ibid., 1927, lxvii, 467.
(13) LURIE, M. B.: Jour. Exper. Med., 1929, l, 747.
(14) BLUMENBERG, W.: Beitr. z. Klin. d. Tuberk., 1929, lxxi, 385.
(15) PAGEL, W., AND HENKE, F.: Lungentuberkulose. In Henke & Lubarsch's Handb. d spec. Anat., 1930, iii, p. 2, 139.
(16) HÜBSCHMANN, P.: Pathologische Anatomie der Tuberkulose. Berlin, 1928.
(17) MEBIUS, J.: Virchow's Arch., 1925, cclv, 416.
(18) OPIE, E. L.: Arch. Path., 1927, iv, 1.
(19) BERNARD, L.: Les débuts et les arrêts de la tuberculose pulmonaire, Paris, 1931.

STUDIES ON THE PATHOGENESIS OF PRIMARY TUBERCULOUS INFECTION[1,2]

II. TENDENCIES IN ADULT PRIMARY TUBERCULOUS INFECTION

HENRY C. SWEANY

In another study (1) an allusion was made to a group of young adults dying of an acute tuberculosis resembling a primary tuberculous infection in every way except that there was a very slight or absent lymph-node involvement. These data seemed to suggest that the uninfected adult, under the conditions of life to-day, does not always react by the same degree of lymph-node involvement that is produced in children or in more primitive types of man. Such findings are not compatible with the doctrine of Ranke and his school (2), Bernard (3), and others, although the same observation has been made by Blumenberg (4), who goes so far as to challenge the whole Ranke scheme and substitute in its stead "disease courses" instead of disease "stages." The advisability of such action must await further work, because the Ranke theory, with its many faults, still remains one of the outstanding contributions in tuberculosis since Koch. It attempts to knit into one fabric the whole disease complex, as no other plan ever has. It has done more than any other scheme to unify the protean manfestations of tuberculosis into one unified whole. Even though to-morrow the whole theory should be thrown aside, it would still remain the superstructure of a more permanent edifice. It is my aim to harmonize the dominant principles of the various authorities with facts rather than to attempt to destroy what is known to be good. For the time being, therefore, I prefer to propose my observations as taking exception to the idea of the usual primary course of tuberculosis that first was observed by Parrot (5) and since amended by a large group of workers up to and including the recent work of Bernard.

If there should prove to be any material difference between childhood and adult infections, the causes of such difference must be sought for.

[1] From the Research Laboratories of the Chicago Municipal Tuberculosis Sanitarium, Chicago, Illinois.

[2] Read in part at the twenty-eighth annual meeting of the National Tuberculosis Association, Colorado Springs, Colorado, June 6–9, 1932.

One theory that is of particular interest is that of changing lymphoid-tissue resistance. Bunting (6), among others, has advanced the idea that the lymphoid tissue is a plastic and ever-changing anatomical structure, according to the age, sex, and physiological status of the individual. He states that "Lymphoid tissue is not equally potent in the two sexes, or at all periods of life." Apparently with a similar idea in mind, Krause (7) compared the difference of adult and childhood tuberculosis to the focalization and course of the infection in the rabbit and guinea pig respectively. The anatomical variations between these two animals' lungs was worked out first by Krause (7). The rabbit seems to possess more of a "closed" type of lymphoid tissue in the parenchyma and along the smaller bronchi; and thus there is not the lymph-node involvement that results in guinea-pig tuberculosis, with relatively slight intrapulmonary lymphoid tissue yet extraordinarily abundant lymphoid tissue in the nodes draining the lungs.

The hint as to human tuberculosis is, therefore, more than a remote one. As the lymphoid tissue changes or is changed, the disease would tend more and more to become localized in the lung parenchyma in human beings.

Another idea that presents itself is the possibility of a changing reaction due to the influences of civilized life. May not there be a tendency to an acquired resistance? And what is more plausible, may not the repeated nonspecific infections (bronchitis, measles, pneumonia, etc.) of civilization produce a changed reaction on the part of the lymphatic apparatus? Will not the nonspecific hilum lymph-node changes observed in childhood, and increasing with age, change the type of tuberculous reaction that may follow? It seems that the possibility is sufficiently great to consider.

CASE REPORTS

Case 1: G. S.; M.T.S. no. 31,096; age 18 years. Born in Wisconsin and came to Chicago at age of 13. She finished High School in June, 1930, and clerked during Saturday afternoons. Her work at school was very hard,—worked on the newspaper staff. General health good as were also home conditions. No history of any social disease, no dissipation and no essential deprivation. Had regular childhood diseases.

Onset pleuritic in March, 1930, with recurrence in July and August. Cough began in April; expectoration in August; night-sweats during the summer; temperature 102°F. Rectal abscess appeared August 10, with loss of weight of 19 lbs.; tiredness, weakness and diarrhoea since the rectal abscess. Died September 13, 1930.

Necropsy Findings: Rather large cavity at apex of right lower lobe, 5 cm. in diameter. Posteriorly and at base of same lobe large, recently formed caseous tubercles and dilated tuberculous bronchi permeate the whole region. Marked infiltration, early fibrosis and "carnification." Many of the caseous tubercles are excavating to form cavities. At bases of both upper lobes is a more acute tuberculosis, progressively more acute in left lower where there is an early disseminated and confluent tuberculous bronchopneumonia. At upper part of right upper is a tuberculous pneumonia in stage of engorgement. Hilum lymph nodes hypertrophic, but show no caseation or calcification.

In the terminal ileum, near the ileocaecal valve, is a small shallow ulcer. Two similar ulcers present in caecum. Peyer's patches in immediate vicinity are much hypertrophied. Lymph nodes draining intestines negative.

The cervical lymphatics negative for tuberculous lesions.

On microscopic examination only acute caseous tuberculous involvement of right lower lobe, with no involvement of hilum nodes except acute hyperplasia. Type of tubercle is more like that of reinfection, but, inasmuch as there was considerable excavation, the first focus had no doubt sloughed out.

Microscopic findings of other organs are cloudy swelling and passive congestion of kidneys, spleen and liver, with fatty changes in liver. No tubercles found. (See plate 1.)

Comment

This patient appears to have acquired her first tuberculous infection that ran a course like an overwhelming primary focus without the lymph-node complex.

Case 2: R. P.; M.T.S. no. 26,024; age 14 years. Patient born in Chicago under good home conditions. General health previous to present illness good. At St. Hedwich's Orphans Home for ten years (until 11 years of age). Acknowledged deprivation, having been helped by an aunt and by County Agent, but dissipation and venereal disease were denied. At six years had whooping cough; at nine years tonsils removed.

Onset insidious, December 14, 1927. At first noticed steady loss of weight, for which patient was sent to Dispensary where diagnosis of tuberculosis was made. Had practically all the classical symptoms of tuberculosis except haemoptysis. At Cook County Hospital from March 26, 1927, until February 24, 1928. Died at our Sanitarium October 1, 1928.

Necropsy Findings: Both lungs consolidated throughout upper two-thirds, and contain numerous thin-walled cavities. An early stage of cavity-formation in upper part of right lower, and large cavities in apex of left lower lobe. Bases of both lobes red and semisolid, with scattered clusters of tuberculous bronchopneumonia. In upper lobes is considerable fibrosis and resorption of active

tuberculous lesions, particularly around some older caseous foci. Difficult to determine any difference in age of these lesions. In upper three-fifths of both lungs there is very little difference in age of lesions. There are small subacute cavities on outer parts of most of bronchial rami of practically the same size, with interstitial infiltration around them but no calcification.

Numerous ulcers, beginning in jejunum and extending to the rectum. Mucosa of the caecum almost entirely destroyed, and wall thickened. Appendix has escaped infection.

Cervical lymph nodes have no calcifications.

Microscopic findings are extreme fatty changes in liver, miliary tubercles of spleen, liver and lymph nodes, and early amyloidosis of spleen.

Comment

This patient appears to have escaped infection until after she left the orphan asylum, when she acquired an infection that appeared like a primary one except for lack of a hilum lymph-node complex.

PLATE 1

FIG. 1. Posterior view of midsection through the lung and bronchi of patient *G. S.*, revealing an acute type of tuberculosis, large cavity in the apex of the right lower lobe posterior, and soft nodular tubercles becoming more acute in distant parts of the lungs. The hilum lymph nodes are hyperplastic but not caseous.

FIG. 2. Microscopic photograph of a cross-section of the right main bronchi, indicated by the arrow in figure 1. Most of the tubercles are entirely secondary in nature. Some have a slight capsule-formation, but at the most could only be considered daughter foci of a primary lesion. $\times 5\frac{1}{2}$

Case 3: A. P.; M.T.S. no 33,364; age 27 years. Born in Sweden; reared in country, and came to United States at 20 years of age. He did factory work for two years. General health good, and patient denies deprivation, dissipation, alcohol, and venereal disease. No past history of illnesses, except occasional colds.

Onset insidious in July, 1931, when patient noted that he fatigued easily, especially in afternoons, and also that he had lost some weight. In September, 1931, went to see physician on account of cough and fatigue. X-ray being taken, referred to Dispensary where advised to take rest. Then entered Sanitarium and failed rapidly until death. Died December 5, 1931.

Necropsy Findings: In lungs, a primary type of lesion at apex of left lower lobe, around which is a small shrunken cavity that shows in roentgenogram (plate 2, figure 1.) From this the disease spreads to apices of lower and right upper, and from here spread throughout both lungs. Small lymph-node complex at hilum of left, corresponding to apex of left lower. No evidence of

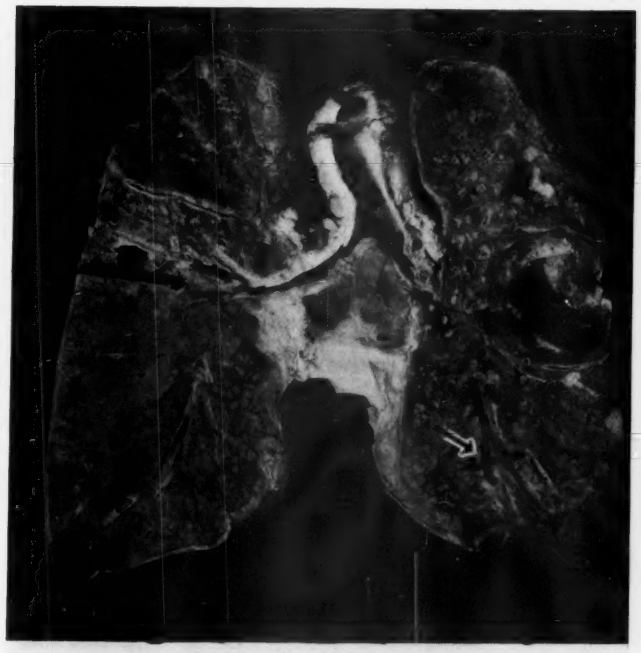


Fig. 1

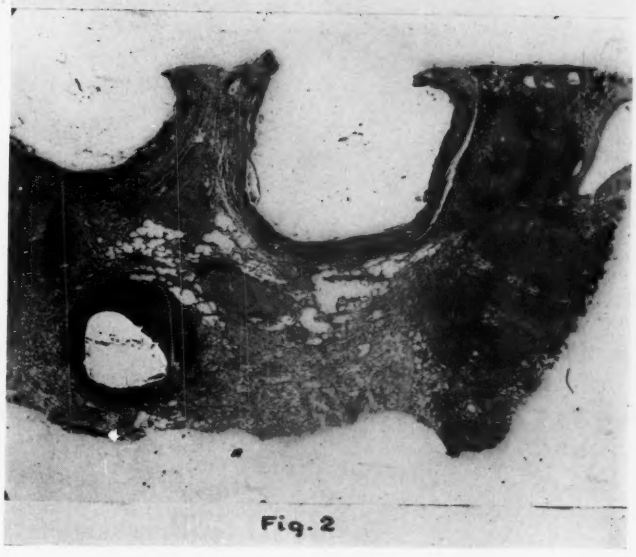


Fig. 2

PLATE 1

haematogenous dissemination. First antemortem radiograph reveals small double cavity, just beneath pleura posteriorly, and corresponding to shrunken cavity found at necropsy.

Numerous longitudinal ulcers in jejunum and ileum, and others in caecum and appendix. Many are narrow, with clear base and firm, heaped-up margins.

Microscopic findings are passive congestion of liver and spleen and tuberculous ulcers of ileum. The large tubercle for section reveals moderately thick capsule and caseous centre resembling those usually found in primary lesions. (See plate 2.)

Comment

Although the tubercle that is shown in the illustration resembles a primary focus, it is not altogether typical and we must grant that the real primary lesion (possibly of the same age) was sloughed out in the cavity. It may be, however, that the lesion shown represents only the

---

PLATE 2

FIG. 1. Copy of a roentgenogram of patient *A. P.*, anterior view, revealing a diffuse tuberculosis throughout the whole right lung with two small cavities at the apex of the left lower lobe posteriorly.

FIG. 2. Section through the region of the cavity of the apex of the left lower lobe posteriorly, revealing a thin-walled compressed cavity, shown by the arrows, and a primary-like tubercle within the rectangle, and various daughter colonies extending out from this localization.

FIG. 3. Microscopic photograph of the tubercle shown within the rectangle of fig. 2. There is an attempted capsule-formation, and slight calcification with definite secondary tubercles surrounding it. While this is not typical of a primary lesion, it resembles it and may be the first daughter colony of a lesion that was excavated in cavities. × 5

---

first daughter focus from the primary one, in a rather rapidly spreading type of primary lesion. It is the oldest tubercle that still remains. Other daughter foci appear in the neighborhood, and range in type from the primary-like, with remaining elastic tissue in the *caseum*, to a pure secondary type.

Case 4: B. C. L.; M.T.S. no. 27,391; age 26 years. Born in Minnesota. She started school at 5½ years of age. At 8 years was out of school for one year on account of rheumatism. Completed two years of normal college; then taught without any loss of time. Came to Chicago in June, 1925, and has been employed in general office work until time of admission to Sanitarium here. Lost no time from work previous to admission. Deprivation and dissipation denied. The patient's eating and sleeping were not good. Slept in a school dormitory about 6½ hours a night. Meals eaten in a cafeteria most of the time. Had

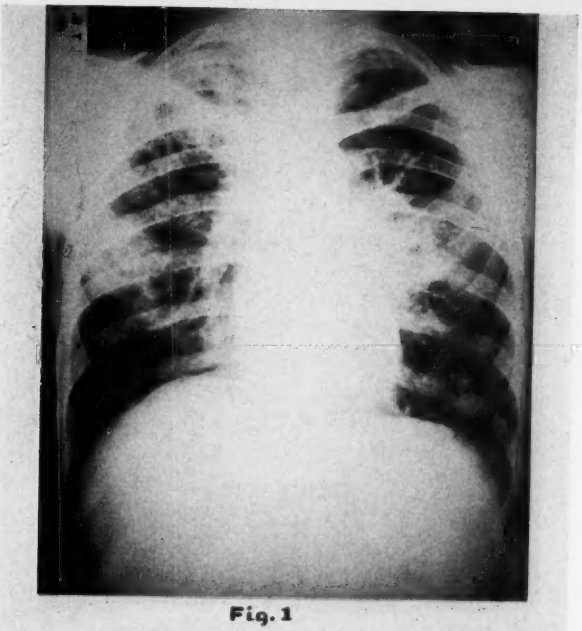


Fig. 1

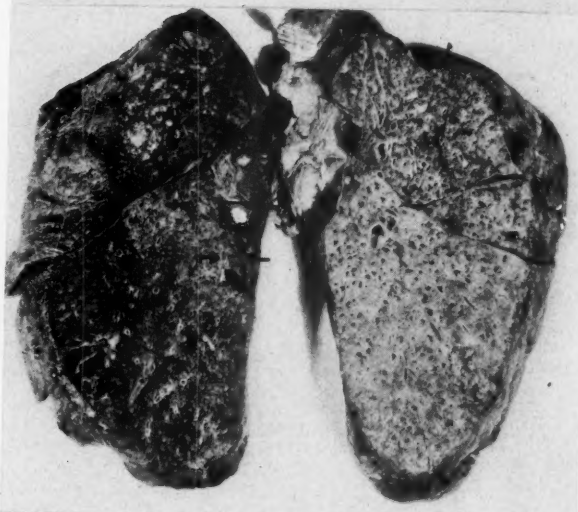


Fig. 2

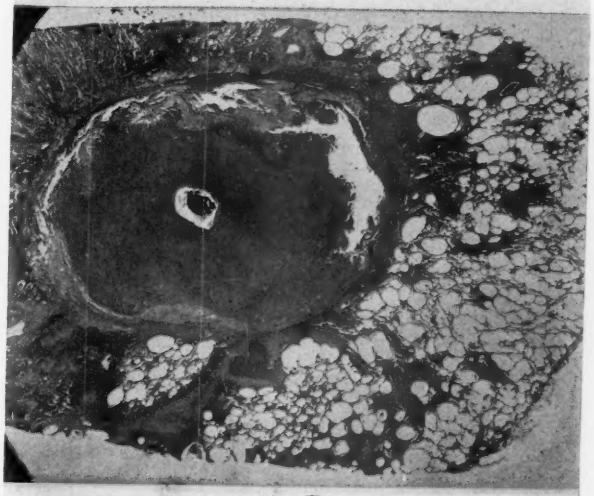


Fig. 3.

measles twice, at ages 16 and 22, and influenza at 12 years. Menstrual history normal. Complains of cough, expectoration, pain in chest, shortness of breath, diarrhoea, and loss of 8½ lbs. Cough began in August, 1928. Also had several night-sweats. Treated, but quickly failed and died November 2, 1928.

Necropsy Findings: In left upper lobe are approximately five lesions that have character of a primary without a lymph-node complex. Some of these have undergone complete caseation and cavity-formation. Practically whole lobe involved. A few scattered miliary tubercles in upper part of lower lobe, as well as in middle and lower lobes on right. Right upper, except apex, contains a caseous pneumonia, undergoing various stages, from engorgement to caseation. No cavity-formation. Hilum and tracheal lymph nodes are enlarged but not tuberculous. A few early infiltrations of calcium, appearing like a primary lesion, in right upper. No calcification anywhere else. Only one very small fibrotic, primary-like lesion in hilum lymph node, measuring about 1.5 mm. across, that can be interpreted as a previous infection (see plate 3, figure 3). There is a definite specific capsule, but lesion too small to produce permanent caseation, so that all was obliterated by fibrosis. In this work we have diligently searched for this type of lesion, thinking that this may be a manifestation of old primaries that could very well be overlooked in the search for calcification.

PLATE 3

FIG. 1. Postmortem radiograph of the lung of patient *B. L.*, revealing multiple cavities in the left upper, with slight calcification and acute pneumonic tuberculosis in the right upper.

FIG. 2. Reveals the calcified lesion indicated by the arrow in fig. 1. There is a peculiar type of caseation and capsule formation here, suggestive of a primary lesion, perhaps in overwhelming dosage, in a slightly or nonimmunized individual. × 5

FIG. 3. Very small fibrotic lesion found in the hilum lymph nodes and the only remaining residue of an early tuberculosis found. The lesion was too small to produce a typical caseation, but is characteristic of a primary tubercle otherwise. × 100

Microscopic examination shows tuberculous bronchopneumonia with caseation and ulceration; marked passive congestion of liver, kidneys, spleen and myocardium; fatty infiltration of liver; and cloudy swelling of kidneys. No tubercles outside of lungs (see plate 3).

Comment

This patient resembles the preceding one except that the lesions are larger and there is evidence of a small earlier infection. The fatal (and essentially primary-like) infection involved the whole left upper lobe in an overwhelming bronchogenic seeding. The dosage of tubercle bacilli was no doubt large, and the type of microörganism may have been un-

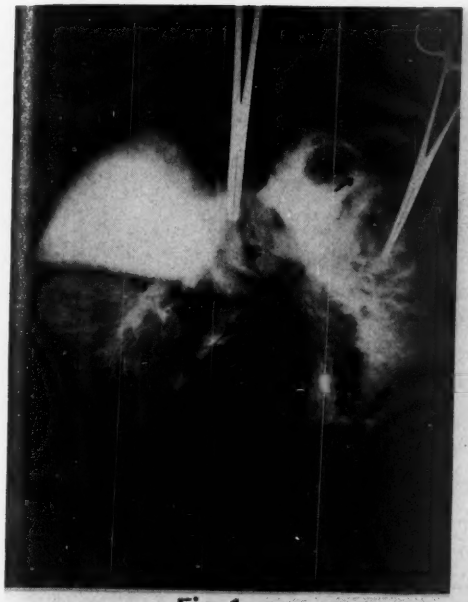


Fig. 1

Fig. 2

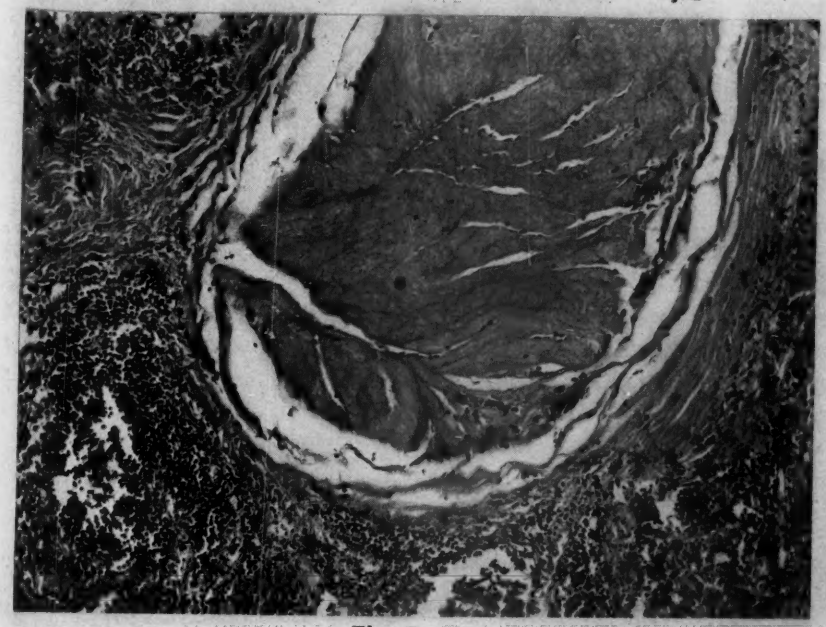


Fig. 3

PLATE 3

usually acute in development. The lesions appeared primary-like because of the tendency to form a specific capsule, as well as a tendency to calcium deposition in some of the caseous centres.

Case 5: C. K.; M.T.S. no. 29,689; age 24 years. Born in Chicago under good home conditions. Her general health good, except for infantile paralysis at three years of age; whooping-cough at 8; measles at 12; scarlet fever at 12 and 14 years, respectively; and diphtheria. No childhood contact with tuberculosis. Attended school until 7th grade and later became an order-filler. Denies deprivation, dissipation and social disease. Quit work October 15, 1929.

The patient's present complaints are cough for two months, expectoration, fever (1 month as high as 102°F.), night-sweats, loss of 24 lbs., tiredness, weakness, dyspnoea on exertion, anorexia, and cramping in abdomen after eating.

Onset pleuritic in May, 1927, with sharp pain on breathing, associated with a cold. Also had night-sweats but no chills. Consulted physician, who informed patient that there was nothing the matter with her lungs. Returned to work but never felt well. Consulted no physician until October, when diagnosis of tuberculosis was made. At this time sputum found positive for tubercle bacilli, and X-ray of chest confirmed these findings. For the past two weeks has had loss of appetite and cramps, and headaches infrequently over the left eye. Insomnia lately. Died February 17, 1930.

Necropsy Findings: Right upper lobe has group of three irregular cavities in middle posterior part. Smallest measures 1.5 cm., and largest about 3 cm. Toward apex posteriorly is bullous emphysematous bleb, about 1.5 cm. in diameter, that communicates with finer bronchiole beneath. One large mass in anterior portion that is soft and caseous, with several clusters posteriorly. Middle lobe normal. Lower lobe contains large irregular mass of consolidation and infiltration, chiefly with red blood cells. Similar basal consolidation in left lower lobe. Left upper lobe contains mass of irregular cavities toward the axillary angle near pleura, and some caseous tubercles near hilum. In the forks of posterior subapical bronchus on left, are numerous caseous, calcified and intrabronchial tubercles resembling primary type of infection. Hilum lymph nodes enlarged, but not caseous. Tracheobronchial lymph nodes moderately enlarged, and on cut-section show no tuberculosis.

There is advanced tuberculous ulcerative enteritis, but no extrapulmonary primary lesions in gastrointestinal lymphatics.

Comment

The reason for presenting this case is because there is a typical primary cluster of lesions in the parenchyma but no hilum lymph-node lesions correspond to such older parenchymal primary residues. The lesions just

mentioned only resemble primary lesions, but they fit into the same group as the others, essentially primary but without lymph-node metastases.

Case 6: Z. C.; M.T.S. no. 29,600; age 18 years. Born in Chicago and lived there all her life. No history of privation and no dissipation. Father and sister have tuberculosis. Has had usual childhood diseases, including influenza at 10, and in 1928 twice. Was in hospital for 2½ months in 1927 with ruptured appendix and was operated on. Since then has never been well.

Onset insidious in April, 1929, followed by night-sweats, chills, loss of 15 lbs., pleurisy on left side, poor appetite, tired feeling since April, 1929, cough, expectoration of one cupful a day, haemorrhage of 4 oz. in September, 1929, diarrhoea, pains in abdomen, belching, vomiting, and rapid pulse. Died February 20, 1930.

Necropsy Findings: In lungs is appearance of adult primary infection. Process seems oldest in bronchi of left lower lobe, where are marked bronchiectasis and ulceration of bronchial walls. There are infiltration of lung parenchyma and peribronchial consolidation toward terminal bronchi. The excavation extends into parenchyma and irregular linear cavities are formed. Toward posterior part are scattering "acinous nodose" tubercles. There is a more acute bronchogenic spread toward left upper lobe, where are numerous irregular linear cavities of all ages, from elementary involvement of bronchi 2 mm. in diameter, tapering toward hilum and terminating in dilated bronchi. There is secondary spread in smaller bronchi around right hilum and one solitary nodule involving a lobule in right apex. There is only slight hyperplastic lymphatic involvement, with no caseation or calcification.

There is advanced acute enteritis, involving jejunum, ileum, caecum and colon.

Microscopic sections reveal no tubercles outside lung and intestines. Oldest lesion in lung is about 7 mm. in diameter, which resembles a primary lesion in that there is well-developed capsule around white *caseum* containing tissue framework as described by Ranke. There is no lymph-nodular complex.

Comment

This again appears to be the primary type of infection in a young adult and is characterized by a lack of lymph-node involvement. The father appears to have infected both children from an exacerbation of an older tuberculosis.

DISCUSSION

The paradoxical problems presented in this work merit careful attention and study. It is certain that there are types of adult primary lesions, as

well as essentially primary lesions in the adult that do not conform to the established doctrines of primary infection. There are wide variations also in children, but here the course is more typical and, when interpreted in the light of virulence and dosage, may be brought into a more systematic classification. *The reason for separating out this type of adult infection is because of the close resemblance to a primary lesion and the high probability of their being primary in character, yet having the frequent lack of a lymphatic and systemic spread.* There is good evidence to believe that the host undergoes a change in "lymphatic resistance" as the age advances, as suggested by Bunting and visualized in animals by Krause. It seems possible that nonspecific infections and "lymphatic intoxications" may cause a nonspecific reactability that helps to bring about this effect. Although the works of Ghon and Ranke, to mention only the more prominent authors, have considered the problem of primary infection, it is obvious that their work does not represent the whole field of primary tuberculous infection. Ghon, in particular, has dealt principally with one phase of it, namely, that of a regressive minimal and perhaps moderately advanced type of lesion. The overwhelming dosage and rapidly growing atypical tubercle bacilli have not been considered. Since this paper was prepared, Sewall, *et al.* (8), have shown that the effect of large dosage in experimental animals tends to produce more of a reinfection type of lesion.

The ordinary course in children, and apparently in adults living a primitive type of existence, consists of a local alveolitis proceeding to healing or sloughing and accompanied by lymphatic involvement, exaggerated more in some than others, and finally a spilling over into the blood-stream, with the development of a variable number of metastases that may pursue one of three courses,—namely, they promptly may become fatal, heal entirely, or become more exaggerated in certain places as isolated secondary lesions (tertiary of Ranke).

In overwhelming doses and apparently in adults, the reaction is entirely different. Blumenberg has pointed out this discrepancy, and, not without some good reasons, has suggested that primary infections must be considered from the standpoint of the various "courses" resulting from the qualitative and quantitative aspects rather than to consider only one type running through a certain set of "stages."

Without going too deeply into the problem, it seems logical that the "stages" of Ranke may be better understood as phases or aspects, especially his first two stages. Ranke's third stage should be considered

under reinfection. It has seemed appropriate to designate these two stages as representing three phases; namely, the local or parenchymal phase, the lymphatic phase, and the haematogenous phase. Practically everyone has conceded them to be a part of every primary infection. The quality of a primary lesion is also rather constant for any particular quantity or quality of microörganism. The extent of time, the degree and the outcome of each, however, are variable. As the time element is usually limited in primary infections by either healing or by reinfections, it leaves only the quantitative aspect to reconcile with the above-mentioned scheme. This will be considered more in a subsequent presentation, but briefly it seems advisable to divide primary lesions into the above-mentioned phases or aspects, and to subdivide them quantitatively into various types or degrees. For example, the first type or degree represents one clear-cut group that is minimal in extent, limited in its course, and definite in its outcome. This type includes a great deal of the reports of Ghon and Küss, and includes most of the old healed primary residues. Pathologically, there is only one age of lesion represented. After a rapid evolution period it is entirely regressive in its course. The second type may be minimal or of moderate quantity, but not limited in extent or outcome. It will show varying numbers and ages of reinfections from within, or exacerbations that spread beyond the borders of the first localizations. It may be progressive or regressive or both in its course. It may be both simultaneously. The third type or degree is when the first infection is large and the course progressive throughout, with rarely a regressive trend. The local lesion is overwhelmingly predominant.

Although this outline is incomplete and at most only tentative, it attempts to suggest a method of classification that incorporates the good in other classes and eliminates the objectionable or controversial features so far as possible. Owing to its brevity it is impossible to cover the whole field or to account for all the phenomena of primary infection.

It will be noted that the "adult type" presented in this paper has not been included in the brief classification given. This type as yet has not been sufficiently established as a separate group to warrant a special grouping. If it can be shown ultimately to be of sufficient importance and incidence, the classification can always be amended. Otherwise, these cases must remain as representing an unusual type, resulting from large dosage, high virulence or some other special character of the parasite. Tentatively, it may be best to list them as third-degree primary lesions.

SUMMARY

A report has been made of 6 primary-like infections in adult individuals that reveal a difference from the usual type in that the lymph-node complex was very small or entirely lacking. The variation is so constant in adult people living in civilized communities that it raises the question of whether it is not the rule in such individuals. A few hints are made toward a more rational pathological classification of primary tuberculous lesions than is represented by existing theories.

REFERENCES

(1) SWEANY, H. C.: Studies on the pathology of primary tuberculous infections, I. The regressive lesions, Amer. Rev. Tuberc., 1933, xxvii, 559.
(2) RANKE, K. E.: Ausgewählte Schriften zur Tuberkulosepathologie, Berlin, 1928.
(3) BERNARD, L.: Les débuts et les arrêts de la tuberculose pulmonaire, Paris, 1931.
(4) BLUMENBERG, W.: Beitr. z. Klin. d. Tuberk., 1929, lxxi, 385.
(5) PARROT, J. M.: Quoted by Ghon.
(6) BUNTING, C. H.: Wisconsin Med. Jour., 1925, xxiv, 305.
(7) KRAUSE, A. K.: Harvey Society lectures, 1921–1922, xvii, 122.
(8) SEWALL, H., DE SAVITSCH, E., AND BUTLER, C.: Nodules of experimental tuberculosis in the guinea pig and their relations to immunity, Amer. Rev. Tuberc., 1932, xxvi, 1.

A STUDY OF TUBERCULOUS INFECTION BY WAY OF THE FEMALE GENITAL TRACT

A Supplementary Report[1]

EDWIN M. JAMESON

In a previous study (1) an attempt was made to determine the nature and frequency of infection when tubercle bacilli of the R1 strain were introduced into the vaginae of healthy nulliparous guinea pigs. A modification of the method used by Bakács (2) was employed and, after careful microscopical study of a large number of sections, it was shown that ascending infections by way of the female genital tract were the rule although lesions in the genital organs themselves were produced but rarely.

The present report is a continuation of the above with animals which had previously been sensitized to tubercle bacilli by the subcutaneous injection of R1 and the subsequent application of a virulent human organism to the vaginal mucosa. As has been established by a number of experiments since Koch's original work in 1890, the secondary inoculation of sensitized animals tends to produce localized lesions and it was hoped that the type of lesions produced, their localization, and the method of spread might be determined when this plan was followed. The results, while falling short of furnishing the desired information in all respects, on account of our lack of accurate knowledge of the lymphatic drainage of the genital organs in the animals used, would seem to be of sufficient interest to warrant this communication.

The method used is essentially that suggested by Bakács, and used in the previous experiment, except that the animals had been sensitized three to four months previous to the vaginal inoculation by an injection into the right axilla of 1 cc. of an emulsion of the R1 strain of the tubercle bacilli which contained 10 to 15 organisms per oil-immersion field. Such an injection in an unsensitized guinea pig tends to produce a primary lymphatic tuberculous lesion at the site of inoculation, which goes on to healing and spontaneous recovery of the animal. It has been shown in the Saranac Laboratory and elsewhere that animals so treated will gen-

[1] From the Trudeau Foundation and the Saranac Laboratory for the Study of Tuberculosis, Saranac Lake, New York.

erally show no evidence of their infection except an involvement of the regional lymph nodes and a positive tuberculin test at the end of six months when R1 is used.

For the vaginal inoculation, 0.5 cc. of an emulsion of a virulent human strain (H37), grown on synthetic media and containing about three hundred (300) organisms to the oil-immersion field, was soaked up on a small cotton tampon, introduced into the vagina through a nasal speculum, and the labia held together with a Michel clip so applied that it did not penetrate the skin. Only those animals are included in the series which lived more than eighty (80) days, the longest duration being in an animal that was killed at the end of one hundred and thirty-four (134) days.

The results obtained confirm the experiments of Bakács (2) and Granzou (3) to a striking degree. Of the 15 animals studied, 9 showed submucous lesions in the vagina, 4 had lesions in the cervix, and one had large tuberculous abscesses in the uterus. In no case were the tubes or ovaries found to be involved. The site of the primary injection in the axilla in all the animals was noted to be fibrous, with occasional small pinpoint caseations.

The question of the lymphatic lesions produced by an ascending genital tuberculosis in the guinea pig is more difficult to elicit in the sensitized animal. If the presence of caseation and microscopical tubercle may be taken as a criterion of reinoculation infection, 9 of 11 animals, in which the iliac nodes were preserved and studied, were positive, and one additional case showed acid-fast bacilli in a smear of the node but no tubercles were seen in the sections examined. The inguinal nodes were examined microscopically in 10 instances and reported positive 8 times; in a ninth animal the lesion was thought to look more like a primary complex. It is presumed that these lesions were due to the reinfection.

The remaining lymph nodes and organs were not studied microscopically and the gross examination showed nothing striking. In 2 cases the axillary nodes on the side opposite the primary inoculation were noted as having pinpoint caseation, two showed caseous paratracheal nodes, two caseous peribronchial nodes, and three showed subhepatic node lesions. The lungs were involved only in the 2 guinea pigs that were killed at the end of 134 days, while the spleen was involved in 5 animals. Tubercles were found in the liver of one of the animals carried 134 days.

The genital lesions produced by the method used were striking in many respects. In the vagina they tended to be localized in the fornices and to spread widely in the submucosa (figure 1, A). Many of the sections

examined were taken serially and in no case was the lining epithelium found to be broken. This is not surprising, as the fornices are more distensible and least liable to injury. While Bakács, Norris (4) and others feel that a break in the mucosa is necessary, this does not seem essential to us. Rather it would seem that the bacilli may penetrate the interstices of the lining cells, establish themselves in the submucous tissues, and later

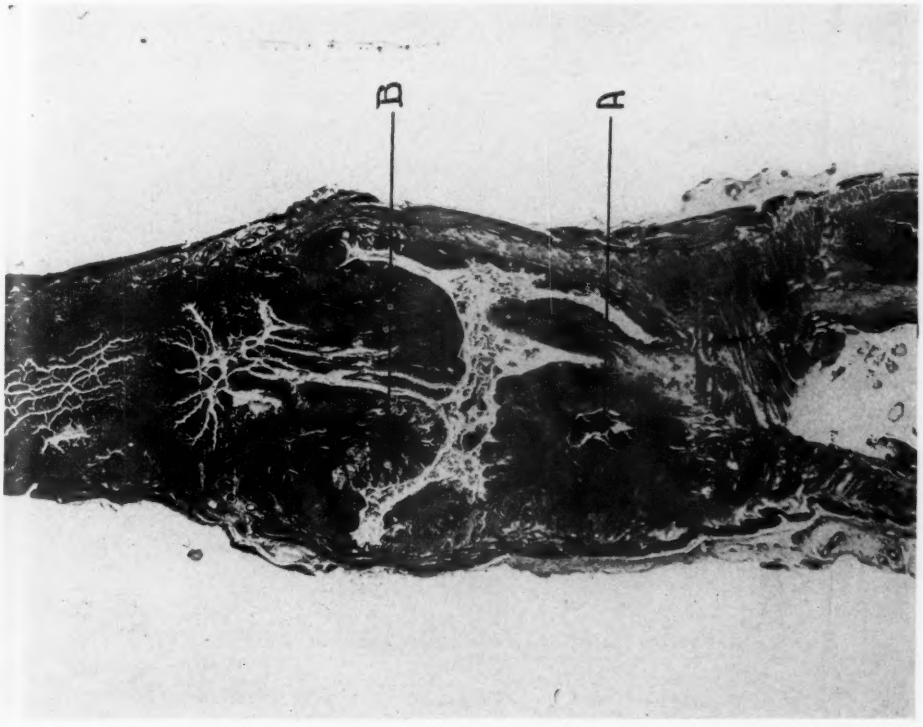


FIG. 1. ANIMAL 5, SHOWING LOCATION OF LESIONS IN VAGINA (A) AND CERVIX (B) IN TYPICAL CASE

ulcerate into the canal in a manner similar to that found in intestinal and laryngeal lesions.

The cervical lesions found in 4 animals were also localized to the deep tissues and did not involve the glands (figure 1, B). Grossly the cervices showed no evidence of tuberculosis and their size did not deviate from the normal. There was strikingly little tubercle-formation, the lesions appearing to be rather diffuse and noncircumscribed, and to be extending upward from the stratified squamous cell-covered *portio vaginalis*.

The single case of uterine lesions was found in an animal that was killed on the 134th day, and showed generalized tuberculosis, with caseous areas in the lungs, spleen, paratracheal, inguinal and axillary lymph nodes, uterus, cervix and vagina. In this animal the uterine tuberculosis was evidenced as soon as the abdomen was opened by the presence of two rounded, yellowish-white elevations, approximately 0.5 cm. in diameter, beneath the peritoneum covering the fundus and the base of the right horn. Microscopically these lesions were found to lie in the myometrium and to be overlaid with a nontuberculous endometrium, which contained

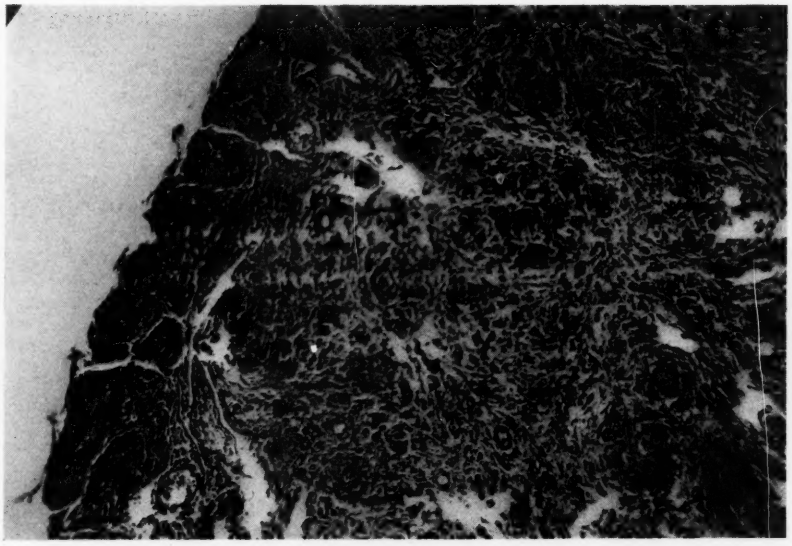


FIG. 2. ANIMAL 6, SHOWING LOCATION OF LESIONS IN WALL OF UTERUS
Serosa shown to left, endometrium (not seen in figure) to right

many cystic glands containing no secretion and which were lined with cuboidal epithelium. The endometrium itself was covered with a single layer of columnar cells, with pale-staining and basally placed nuclei. In some parts the endometrium contained but few blood-vessels; in others the vessels were dilated and engorged. The tuberculous inflammation was most intense beneath the serosa and in some sections had destroyed the muscle. (Figure 2.)

These findings in the vagina, cervix and uterus can be explained only on the basis of a lymphogenic spread, and the possibility of a surface or intracanalicular dissemination would seem to lack demonstration, although

Granzou (5) has noted that after infection of the lumen of the uterus (presumably in unsensitized guinea pigs) the peripheral layer of the uterus becomes involved more often than the central layers, while after an intrauterine reinfection the uterus may react with an endometritis. It would further seem probable that the lower genital tract in the guinea pig has a lymphatic drainage distinct and separate from that of the upper tract, although both may eventually empty into the same regional lymph nodes.

The changes found in the endometrium and ovaries of animals dead of tuberculosis are evidence of the profound alterations in the pathological physiology of the bodies infected with this disease, and offer a fruitful field for studying the basis of the menstrual difficulties of tuberculous women. A study based upon experiments in animals and postmortem human material is now in progress: suffice it that anatomical abnormalities, as evidenced by an atrophic condition of the endometrium, with a round-cell, interglandular hyperplasia and a rather high incidence of cystic glands, combined with follicular cysts and evidence of disturbed ovulation in the ovary, are present in a high percentage of cases. For want of a better name the microscopical appearance of the endometrium in these cases has been designated a "toxic endometritis," and its occurrence in human beings noted by Norris and in animals by Granzou. Its nature is unknown.

CONCLUSIONS

1. Fifteen animals, previously sensitized with tubercle bacilli, were reinfected by placing a tampon soaked in an emulsion of human tubercle bacilli in the vagina.

2. Nine of the animals so treated developed vaginal, four cervical, and one myometrial lesions.

3. The method of spread of ascending genital tuberculosis would seem to be by way of the lymphatics.

4. The infrequency of upper genital infections after vaginal inoculations and the difference in their nature, where found, from the common clinical uterine tuberculosis would seem to indicate that uterine and tubal tuberculosis is seldom or never an ascending infection.

5. Similarly, the rarity of cervical and vaginal tuberculosis in the human being, in which upper genital-tract tuberculosis is said to constitute about 8 per cent of all cases of salpingitis, would indicate that these lesions are not produced by a haematogenous or descending infection and

the probability of an ascending type of infection must be taken into consideration, as vaginal lesions are apparently easily produced by the application of tubercle bacilli to the vaginal mucous membrane.

BIBLIOGRAPHY

(1) JAMESON, E. M.: A study of tuberculous infection by way of the female genital tract, Amer. Rev. Tuberc., 1932, xxv, no. 2.

(2) BAKÁCS, G.: Experimentelle weibliche Genitaltuberkulose, Archiv. f. Gynäkol., 1927–1928, cxxxi, 364.

(3) GRANZOU, J.: Experimentalarbeiten über weibliche Genitaltuberkulose, Med. klin. Wchnschr., 1928, xxiv, 21.

(4) NORRIS, C. C.: Gynecological and obstetrical tuberculosis, D. Appleton & Co., 1924.

(5) GRANZOU, J.: Tierexperimentelle Studien über Ablauf weiblicher Genitaltuberkulose im graviden, puerperalen, und allergischen organisms, Beit. z. Klin. d. Tuberk., 1928, lxx, 548.

THE PRODUCTION OF TUBERCULOUS TISSUE AND HYPERSENSITIVENESS TO TUBERCULIN IN GUINEA PIGS[1]

C. H. BOISSEVAIN

It has long been known that dead tubercle bacilli after intraperitoneal injection into guinea pigs cause hypersensitiveness of the same type as that which is caused by living bacilli. The time that elapses between the intraperitoneal injection and the appearance of hypersensitiveness is the same in both cases; the tissue response is identical; epithelioid and giant cells are found, arranged in typical tubercles. The only difference between the lesions caused by living and by dead bacilli is that those by the former are progressive. In experiments on hypersensitiveness we may use heat-killed bacilli as our point of departure, as the property of producing hypersensitiveness is not noticeably affected even by autoclaving.

The appearance of hypersensitiveness is apparently very closely connected with the production of tuberculous tissue. Baldwin (1) and Krause (2) have claimed that tissue allergy to tuberculin is always accompanied by anatomical tubercle somewhere in the body. A different point of view is held by Sabin and her co-workers (3); they think that the power to provoke the formation of tuberculous tissue resides in certain fatty acids with high molecular weight. The most active of these fatty acids is contained in the phosphatide of the tubercle bacillus. They failed, however, to find any hypersensitiveness to tuberculin in rabbits, in which tuberculous tissue had been produced through the injection of the phosphatide and other lipoids.

In a previous publication (4), I have described a method for preparing a phosphatide from the tubercle bacillus, which very closely resembles Anderson's phosphatide A3 (5) in melting-point and phosphorus content, but which produces neither tuberculous tissue nor tuberculin hypersensitiveness in the guinea pig. In isolating the active substance from the tubercle bacillus quantitative relationships are most important. Before any substance derived from the tubercle bacillus may be recognized

[1] From the Laboratory of the Colorado Foundation for Research in Tuberculosis at Colorado College, Colorado Springs, Colorado.

as the cause for the appearance of tuberculous tissue, we must require that the substance in question is at least as active in producing this tissue as the tubercle bacillus itself. Sabin, Forkner and Doan (3) used 80 mgm. phosphatide in their experiments on rabbits, corresponding to 1.6 gm. tubercle bacilli. If the phosphatide were the only active part of the tubercle bacillus, 80 mgm. should be as active as 1.6 gm. dead tubercle bacilli. If the phosphatide is only one of many active constituents of the tubercle bacillus it should be at least as active as 80 mgm. dead bacilli. No evidence has been published by them to show whether this phosphatide is more or less active than the dead bacilli.

If the phosphatide is less active than the original tubercle bacilli it is not necessary to assume that a separate substance is responsible for the formation of tuberculous tissue and for tubercle hypersensitiveness. An impurity may be present in sufficient amount to provoke the formation of some tubercles, but not sufficient to cause hypersensitiveness.

Anderson's phosphatide A3, which was used by Sabin, is prepared by making an ether extract of tubercle bacilli and precipitating this several times with acetone. I proposed a further purification by dialyzing and subsequently dissolving the phosphatide in a mixture of water, alcohol and ether, and then filtering through a Mandler filter (4). This filtration is a more satisfactory way of removing bacillary débris (both acid-fast and non-acid-fast) than filtration in ethereal solution. Some tubercle bacilli always pass through when an ethereal solution is filtered, even when the filter is completely impassable for the same bacteria in aqueous suspension. It seemed of some interest to investigate if an increase of activity takes place during the different stages of purification, and if the increase (or decrease) in the power to provoke the formation of tuberculous tissue and skin hypersensitiveness to tuberculin go parallel or not.

Guinea pigs were injected with 20 mgm. of each of the following substances:

1: Dead tubercle bacilli, human, strain H37.
2: Ether extract of tubercle bacilli, filtered through Mandler filter (medium porosity) and evaporated.
3: Same extract after three precipitations with acetone (this product corresponds to Anderson's phosphatide A3).
4: Same extract after further purification by dialysis and filtration through Mandler filter in water-alcohol-ether solution.

After three weeks all the guinea pigs were skin-tested with 0.2 cc. of a 0.2 dilution of Old Tuberculin; 48 hours later they were killed and examined for the presence of anatomical tubercle.

1: The animals receiving dead bacilli showed a marked skin reaction, infiltration and redness of more than 20 mm. diameter, with necrotic centre. Most of the tissue reaction was in the omentum, which formed a solid clump of tuberculous tissue, averaging 5 cm. long and 2 cm. in diameter.
2: The animals treated with the crude ether extract showed a skin reaction as marked as those treated with the dead bacilli, but only about half as much tuberculous tissue (5 cm. x 1 cm.).
3: Animals treated with the precipitated extract showed a doubtful skin reaction; infiltration and redness of about 1 cm. in diameter, but no central necrosis. The omentum was much shortened and shrivelled up in many places, apparent remnants of an inflammation that had mostly disappeared at the time of death. After careful search a few microscopical tubercles were found.
4: Animals treated with the completely purified product did not show any trace of tuberculin reaction or any anatomical tubercle in the omentum or elsewhere.

At no stage of its preparation is the phosphatide more active than the tubercle bacilli from which it has been prepared. On the contrary, a little of the activity disappears at each step in the preparation, until we finally arrive at a product which gives neither skin sensitiveness nor the formation of tuberculous tissue. It is especially interesting to see that the power to produce tuberculous tissue and tuberculin hypersensitiveness disappears simultaneously, in agreement with the views of Krause.

The crude ether extract contains some acid-fast bacilli, but not nearly enough to account for the tremendous hypersensitiveness it produces. The amount of tuberculous tissue is also more than could be expected on account of the few bacilli in the extract. It seems likely that the non-acid-fast forms of tubercle bacilli, of which we see many in most cultures of the tubercle bacillus, accumulate in the ether extract. The possibility exists, however, that apart from these bacilli and bacillary débris, the crude ether extract contains another substance which is responsible for its somewhat unexpected activity. However this may be, the activity disappears mostly during the following purification, and the phosphatide, prepared according to Anderson's directions, is very much less active than the corresponding amount of dead bacilli. It is certainly more probable that this feeble activity is the result of a remaining impur-

ity than that it constitutes an attribute of the phosphatide. As a matter of fact, further purification can remove this impurity without materially changing the composition of the phosphatide.

The foregoing results show that we are not obliged to give up the idea that tuberculin allergy and the formation of tuberculous tissue are intimately connected as different manifestations of one single phenomenon. It is fairly well established that the active principle of tuberculin is of a protein nature. For this reason it seems highly probable that the principle that causes tuberculin hypersensitiveness and tubercle-formation is of the same nature. Most of the recent studies on tuberculin have been occupied with the water-soluble, non-heat-coagulable protein. It must not be supposed that this is the only protein with a tuberculin-like nature. A heat-coagulable protein and an alkali-soluble protein are well known; both are active tuberculins. After every possible extraction a considerable amount of insoluble material remains. This material contains an insoluble protein, which has all the properties of the original tubercle bacilli; it acts as a tuberculin, causes hypersensitiveness in normal animals, and provokes the formation of tuberculous tissue. The insoluble protein is a more complete antigen than the soluble protein. The latter can provoke the skin reaction in a tuberculous guinea pig, but is unable to cause the formation of tuberculous tissue or to render a guinea pig hypersensitive, while the former has all these properties. To prove the assumption that the insoluble protein is responsible for most of the effects of the tubercle bacillus, it would be necessary to obtain this insoluble protein in a completely pure state. At the present time it does not seem possible to do this. Some preliminary experiments in our laboratory have shown, however, that it is possible to condense the water-soluble protein into an insoluble substance by the use of formaldehyde. Water-insoluble protein does not provoke the formation of tuberculous tissue but the water-insoluble material, that precipitates after two weeks in formalin, does.

SUMMARY

1. During the purification of the phosphatide from the tubercle bacillus, the power to provoke the formation of tuberculous tissue and the power to cause hypersensitiveness to tuberculin are lost simultaneously.

2. No concentration of the material that causes the formation of tuberculous tissue takes place during the preparation of the phosphatide.

3. Most of the biological activity of the tubercle bacillus remains in the residue remaining after removal of the lipoids, carbohydrates and soluble protein. This residue contains an insoluble protein.

REFERENCES

(1) BALDWIN, E. R.: Tr. Nat. Assoc. Study & Prev. Tuberc., 7th annual meeting, 1911, p. 351.
(2) KRAUSE, A. K.; Bull. Johns Hopkins Hosp., 1911, xxii, 250; Amer. Rev. Tuberc., 1925, xi, 343.
(3) SABIN, DOAN AND FORKNER: Jour. Exper. Med., 1930, lii, supplement no. 3.
(4) BOISSEVAIN, C. H., AND RYDER, C. T.: Amer. Rev. Tuberc., 1931, xxiv, 751.
(5) ANDERSON, R. J.: Jour. Biol. Chem., 1927, lxxiv, 525.

A STUDY OF SO-CALLED SKIN LESIONS OF TUBERCULIN-REACTING CATTLE

LYMAN L. DAINES[1] AND HAROLD AUSTIN[1]

In 1930, 84,620 head of cattle were tuberculin-tested in Utah and, of these, 622 were condemned as reactors. Fifty-one of these gave evidence, on postmortem examination, of systemic lesions of tuberculosis, while 571, or 91.8 per cent, showed either skin or subcutaneous lesions only, or no visible lesions were found. Of the reactors 63.3 per cent were found to be in the so-called skin-lesion group and gave no visible evidence of lesions elsewhere.[2]

Data from other parts of the United States reveal a condition somewhat similar to that found in Utah, and thus help to emphasize the need of more definite knowledge as to the aetiology of so-called "skin-lesion tuberculosis."[3] Also, because of the apparently high incidence of no-lesion reactors, it is important that additional information concerning these be obtained. It is recognized that possibly many of these no-lesion cases may, on detailed microscopic examination, reveal microscopic lesions. Still it is difficult to believe that all of them can be explained on this basis. Evidence that has been obtained as a result of the accreditation work since 1917 strongly points to the possibility that many of the no-visible-lesion reactors as well as many of the skin-lesion cases must be explained on a basis other than tuberculosis.

Since the tuberculosis eradication work was undertaken there has been a marked reduction in the percentage of cattle which react to the tuberculin test as well as a marked decrease in the percentage of the reacting cattle which show advanced lesions. At the same time there has been no actual decrease in the percentage of cattle which belong to the no-visible-lesion and skin-lesion groups. On the contrary, there has really been a very marked relative increase in these groups if one considers

[1] Department of Bacteriology and Pathology, Medical School, University of Utah, Salt Lake City, Utah.

[2] Data furnished by Dr. F. E. Murray, U. S. Bureau of Animal Industry.

[3] The term "skin lesion," as used in this paper, refers to both skin and subcutaneous lesions.

only the tuberculin-reacting animals. Furthermore, many veterinarians experienced in tuberculin testings report that many herds which have no record of tuberculosis, either before or after testing, furnish occasional or repeated cases of tuberculin reactors. It is becoming obvious as time goes on that a very large majority of these cases are of the no-visible-lesion or skin-lesion types.

While the factors mentioned above are very strongly suggestive of some agent other than the tubercle bacillus as the cause of the tuberculin reaction, it would be interesting, if possible, to obtain direct experimental evidence as to the aetiological agent. As applied to so-called skin tuberculosis, this is the purpose of the present work.

Since 1915 many workers in different laboratories have been making determined efforts either to cultivate the causative organisms of the skin lesions or, by animal inoculations, to obtain some information as to their nature. It is probably true that our actual knowledge at the present time concerning this problem, notwithstanding this large amount of work, is about the same as when the work was begun.

Traum (1) was the first in this country to report the finding of an acid-fast organism in skin lesions, and, in 1919 (2), he succeeded in obtaining a culture of an acid-fast organism from a typical case. He was unable to produce lesions in guinea pigs and rabbits with this organism and was therefore led to consider the organism as not being a true mammalian tubercle bacillus. Again, in 1923 (3), Traum reported the demonstration of acid-fast organisms in two out of three cows which gave positive intracutaneous tuberculin reactions and which also had well-developed subcutaneous nodules. Guinea pigs inoculated from these nodules failed to develop tuberculosis. A pleomorphic gram-positive organism which failed to react uniformly to the acid-fast stain was cultivated from these lesions. Although he made many attempts, Traum was unable to obtain this organism from any other case.

In 1922, J. G. Olson, working in our laboratory, succeeded in obtaining a culture of an acid-fast organism from a typical skin lesion. We failed to obtain successful animal inoculations with this organism.

Beach and Hastings (4) reported unsuccessful attempts to obtain cultures or animal inoculations from 54 skin lesions from as many tuberculin-reacting cattle.

Carpenter and Goldberg (5) failed in attempts to infect guinea pigs, rabbits and chickens with extracts from bovine skin lesions. Nodular skin lesions were produced by them by the inoculation of bovine tubercle bacilli into the skin of cattle.

Crawford (6) concluded that several factors seemed to indicate other acid-fast organisms than the bovine tubercle bacillus as the causative organisms in "skin-lesion" tuberculosis.

Mitchell (7) failed in many attempts to cultivate an acid-fast organism directly from skin lesions, although he described an acid-fast pleomorphic organism in the lesions. After about 100 unsuccessful attempts to infect laboratory animals from skin lesions, he finally succeeded in infecting a rabbit which died in 131 days. Cultures of an acid-fast organism were obtained and these produced, on inoculation into a calf, a lesion which had the appearance of a skin lesion.

Van Es (8) subjected 40 different sets of skin lesions to typing experiments and concluded that "apparently no living tubercle bacilli were present."

Traum, in 1928 (9), attempted a large number of animal inoculations from 38 different cows with skin lesions only. A rabbit developed a nodule in the lung, which yielded a large number of acid-fast organisms. A guinea pig obtained a typical Preisz-Nocard infection. Traum had previously (10) reported the finding of the Preisz-Nocard bacillus in two typical skin lesions.

Hastings, Beach and Thompson (11) obtained a number of cultures from the tissues of no-lesion tuberculin-reacting cattle. These cultures which produced no lesions in cattle, guinea pigs, rabbits and fowls, when injected into tuberculosis-free cattle, caused a sensitization to tuberculin. These workers state that "from the evidence available it seems safe to conclude that all or nearly all skin lesions are due to other than tubercle bacilli."

Day (12) reported negative results in approximately one hundred attempts to obtain, from skin lesions, cultures on Petroff's medium. He succeeded, following several attempts to inoculate different kinds of animals from bovine skin lesions, in infecting a calf with what he considered true tubercle bacilli.

Van Es (13) was unable to infect tuberculosis-free hogs by feeding them a considerable amount of bovine skin lesions.

Crawford (14) failed in all attempts to grow acid-fast organisms on artificial media or to cause lesions by inoculation of sections of skin lesions into guinea pigs, rabbits, mice, rats, chickens and cattle. In this paper he reported failure in attempts to produce skin lesions in cattle by the use of *B. phlei*, the Mist bacillus, the "hog skin" bacillus, and the avian and the human tubercle bacilli, although he had pre-

viously reported the production of fairly well-marked tuberculin reactions in cattle following injections of the first three organisms. Bovine tubercle bacilli, inoculated into the abraded skin of the one bovine animal so treated, produced only internal lesions of tuberculosis.

Elder and Lee (15) produced local lesions in 3 cows by subcutaneous injections of avian tubercle bacilli, and these animals reacted to mammalian tuberculin when injected intracutaneously. The Royal British Commission had previously produced local lesions in cattle and hogs by subcutaneous injections of avian tubercle bacilli.

Group tuberculin reactions were demonstrated by Hagan and Ziessig (16) who showed that avian tuberculin apparently gave results identical with those obtained with johnin when applied to cattle and other animals naturally or artificially infected with the organisms of Johne's disease.

Funk and Huntoon (17) obtained skin reactions in about 95 per cent of their human tuberculous patients with the protein fraction of the timothy-grass bacillus. Several workers have shown that a water-soluble protein is apparently one of the common fractions of the acid-fast family and that this is the substance in tuberculin which is responsible for the skin reaction.

Feldman (18) isolated avian tubercle bacili from the brain of a rabbit which had received an intracerebral injection of an emulsion from a bovine skin lesion. The carcass from which this lesion was taken contained gross lesions of tuberculosis in lymph nodes in several different places.

The writers (19) reported the close similarity between our group-2 organisms and the Preisz-Nocard bacillus of caseous lymphadenitis of sheep, and also pointed out the tendency of the Preisz-Nocard bacillus to take on acid-fast properties in media rich in lipoids. They further pointed out the close resemblance between the organisms from bovine skin lesions and the organism isolated by Walker and Sweeney (20) and others from human and rat leprosy.

LESIONS AND MICROÖRGANISMS ISOLATED FROM THEM

This is a partial report of the study of skin lesions from 225 animals, 75 per cent of which had given positive tuberculin reactions. The remaining 25 per cent had not been tested.

The specimens as they reach us consist of strips of skin and subcutaneous tissue containing the lesions undisturbed. Each specimen contains from one to several nodules, mainly subcutaneous, varying from

pin-head size to as large as an ordinary hen's egg. There are three general types of nodules with the following gross appearance: (1) Granulation tissue with no apparent necrosis, (2) central necrosis without calcification, and (3) central necrosis with calcification. In the second and third types the centres usually contain a thick, semifluid, odorless material which usually varies from greenish-yellow to orange. Often dense cords connect several nodules in chains, and these cords may contain similar necrotic material.

The lesions are opened from the under surfaces through thoroughly cauterized tissue, and cultures and microscopic smears are made. These are not obtained from the necrotic material, but must be secured from scrapings from the wall of the abscesses or from tissue from the wall ground in a mortar. The staining of smears and cultures is carried out by ordinary Ziehl-Neelsen methods, care being taken to secure thorough decolorization by means of 3 per cent HCl in 95 per cent alcohol.

With the exception of one culture of the bovine tubercle bacillus, all of the cultures obtained develop equally well at room temperature and at temperatures up to 37°C. They grow under aerobic conditions and on various kinds of rich media. We have come to use almost entirely a Petroff's medium modified to contain more moisture, less gentian violet and no glycerine. Cultures are furnished with a small amount of carbon-dioxide and the tubes are sealed with paraffin.

Acid-fast organisms are found in every typical lesion from reacting cattle, varying in number from one in several fields to large numbers in a single field. These acid-fast organisms vary in morphology from coccoid and diplococcoid forms to short or long, straight or curved rods (solid or beaded) and diphtheroid forms of various sizes and shapes. The most constant acid-fast form is a solid, medium-sized, straight rod about the size of a typical bovine tubercle bacillus.

All the morphological forms mentioned above are also found in various lesions without having retained the fuchsin stain. The most constant non-acid-fast forms are the diplococcoids which occur usually in small numbers in nearly every typical lesion from reacting cattle. For some time we naturally concluded that these different forms represented separate species, but as the work continued we became convinced that we were perhaps dealing with a markedly pleomorphic species which may be either acid-fast or acid-sensitive.

Our cultures up to the present time seem to fall into four fairly definite groups on the modified Petroff's medium:

Group 1: A typical bovine tubercle bacillus obtained from an animal which had internal as well as skin lesions.
Group 2: Dry, rough, friable colonies, varying from nonchromogenic to cream color, yellow, red and dark brown. Growth appears in 24 to 48 hours. At first most of the organisms are acid-sensitive but in some of the cultures a few may have acid-fast properties, the degree of acid-fastness and the numbers concerned usually increasing as the cultures become older. A few of the strains of this group after months of cultivation have failed to show acid-fast properties. This group appears from practically all the lesions.
Group 3: Deep orange, smooth, moist colonies; growth appearing from lesions usually in about seven weeks, subcultures appearing earlier. Nearly all of the organisms in these cultures are acid-fast from the beginning and remain so indefinitely. We have obtained 23 pure strains of this type.
Group 4: Colorless, smooth, moist, spreading colonies; growth appearing in about 48 hours. These organisms are non-acid-fast. This group has always accompanied group 3 in our cultures.

The morphology of the organisms in cultures is as follows:

Group 2: On modified Petroff's they are, from the beginning, diphtheroids with a variable number (two to six) of deep-staining granules. Later, as they become acid-fast, they tend to develop involution forms, becoming clubbed at the ends or swollen at the centres. There are always fairly large numbers of straight acid-fast rods. Some of the short diphtheroids appear to be diplococcoids.

When this form is grown in litmus milk, inspissated egg-yolk, or lactose broth, acid-fastness increases more rapidly, and many coccoid, diplococcoid and streptococcoid forms appear. These forms appear larger than they do on Petroff's medium. They are gram-positive.
Group 3: On Petroff's medium they vary from large rods (either solid or beaded) to short, solid forms or diphtheroids. They are gram-positive.
Group 4: On Petroff's medium they vary from short, solid diphtheroids to large bacilli and coccoid forms. They are gram-positive.

Fermentation reactions of group 2 in the common sugars are variable. All of Walker's diphtheroid groups of human and rat leprosy are represented in these fermentations. In addition to these we have at least one other fermentation group. Group 3 has given no fermentation reaction.

ANIMAL INOCULATIONS

The following animals have been used: Guinea pigs, rabbits, white mice, wild rats, white rats, cows and chickens.

Rabbits and chickens have failed to give any evidence of gross changes.

In a few cases the rabbits died early. The chickens have failed to respond to the injection of avian tuberculin. Four male rats out of twelve died from four to six months after inoculation. The principal postmortem findings consisted of firm nodules at the point of injection. A marked alopoecia developed in about sixty days after inoculation, but this later disappeared, to reappear on second inoculation. Recently a wild rat died 401 days after its first injection with a group-3 organism and 39 days after a second injection. At the point of inoculation there was a caseous lesion, about 1 cm. in diameter, smears from which showed many acid-fast diphtheroids. There were also many small caseous nodules in the upper lobes of both lungs. Microscopic smears of these contained many large streptothrix-like, non-acid-fast organisms. Cultures produced an organism morphologically identical with group 4.

Guinea pigs, inoculated with material direct from the lesions, have yielded no results. Most of the guinea pigs injected with our groups 2, 3, and 4 have died within 14 to 235 days. In every case the inguinal lymph nodes have been moderately enlarged and injected, and organisms resembling the strains injected have been recovered in cultures in most cases. The adrenals have been moderately to deeply injected. Apparently the same organisms have been recovered in culture from the kidneys and heart's blood of animals dying within two months after inoculation.

Whenever group 3 has been used for subcutaneous inoculation, there has practically always been produced a firm nodule or a less firm abscess at the point of injection. In a few cases this was also true when group 2 was used. Organisms of the respective groups were recovered in culture from these lesions. If intraperitoneal injections were made there was a small abscess in or under the peritoneum where the needle had passed through. Five of the male animals had small to fairly large abscesses in the testicles or in the enveloping membranes. In 3 cases what appeared to be a fairly typical pseudotuberculosis was produced in the liver, on the peritoneum, and in the enveloping membranes of the testicles. Cultures of organisms morphologically similar to the ones injected were obtained in all of these cases. Positive reactions to mammalian tuberculin developed in a large percentage of the guinea pigs tested.

Eight white mice, injected with group-3 organisms, died within 30 to 40 days. They had several small, nodular, subcutaneous, caseous lesions at and near the point of injection. They also had small caseous and calcareous lesions in the liver. In one case there were a few small

gray flakes in the enveloping membranes of the testicles. Cultures resembling group 3 were obtained in several cases from the lesions in these mice.

On August 31, 1931, eight cows received injections of various strains and combinations of strains. In all, 22 inoculations were made intracutaneously, subcutaneously, into the teats, into the prescapular lymph nodes, and by scarification into the skin. Four of the cows received one or two subsequent injections.

The animals that received group-2 organisms alone developed swellings which soon disappeared. The ones that were given group-3 organisms, whether alone or in combination with group-2 or group-4, developed subcutaneous nodules which persisted for some time, and, in a few cases, these nodules were still present nine months after the first injection. In one animal a subcutaneous nodule on the leg and one on a teat are giving evidence of definite growth and probably of extension, and experienced veterinarians have stated that they are typical skin lesions. The animal with these lesions has given slightly positive intracutaneous tuberculin reactions on three different occasions, while three tests have been negative.

One of the cows inoculated with a group-2 strain, after becoming markedly emaciated and too weak to stand, was killed on November 10, 1931. Autopsy revealed multiple lesions in the liver, heart muscle and kidneys, varying from 2 mm. to 2 cm. in diameter. The centres of these lesions contained greenish-yellow, odorless, thick, necrotic material, microscopic smears of which showed a few diplococcoid or diphtheroid gram-positive and non-acid-fast organisms. Cultures yielded an organism agreeing in every respect with the one inoculated. Intracutaneous tuberculin injection in this animal four days before she was killed failed to give a reaction.

Similar cultures were obtained from the swollen knee-joint of one of the animals which had received group-2 organisms.

Several cows have been injected subcutaneously with a virulent strain of the Preisz-Nocard bacillus. In most cases abscesses have formed at the site of the injection, which have ruptured and drained. In a few cases no rupture occurred, and hard subcutaneous nodules have persisted for some time. Some of these animals have given a slightly positive reaction to the intracutaneous injection of mammalian tuberculin. Reactions have been negative at other times.

We shall not attempt at this time to give a description of the histo-

pathology of the lesions. Early experimental lesions resemble very much the early spontaneous lesions of caseous lymphadenitis of sheep caused by the Preisz-Nocard bacillus. We have no opportunity to study older lesions from sheep. Older spontaneous skin lesions from cattle present the typical histological picture of tuberculous tissue.

DISCUSSION AND SUMMARY

Whenever careful search is made of microscopic smears taken from skin lesions of tuberculin-reacting cattle and stained by the Ziehl-Neelsen method, it is possible to find, from practically all lesions, acid-fast and usually also non-acid-fast organisms of different shapes and sizes. By using a modified moist Petroff's medium and adding a small amount of carbon-dioxide, cultures may be obtained routinely from these lesions, which are either acid-fast from the beginning or which develop acid-fastness on certain culture media. These cultures consist of pleomorphic, coccoid, diplococcoid, diphtheroid or solid rod-shaped organisms. These various forms seem to represent different stages of a pleomorphic organism which may be obtained usually in pure culture. Because of these facts and also because of other evidence given, we think it is probably the cause of the lesions.

Fairly characteristic skin lesions have been produced experimentally by injecting acid-fast strains of these organisms into rats, white mice and guinea pigs, while in cows typical lesions have resulted. Tuberculin tests in guinea pigs have been, for the most part, positive, while in cows the reaction is not constant, varying from negative to suspicious. This reminds one strikingly of results obtained in routine tuberculin-testing in the fields, where many skin-lesion cows will vary over a period of time between positive, suspicious and negative reactions.

Internal lesions produced in rats, white mice, guinea pigs and cows resemble more nearly pseudotuberculosis of sheep produced by the Preisz-Nocard bacillus. Although in some animals there has been some orchitis, this has not been as strikingly typical as that produced by virulent Preisz-Nocard organisms.

Organisms similar to the ones injected into the experimental animals have been consistently recovered in culture from the experimental lesions.

Chickens have so far failed to respond in any way to the injection and feeding of the organisms.

The identification of the organisms in question has not been made.

The following possibilities must still be kept in mind. They may be either:

(1) Modified Preisz-Nocard or similar bacilli, or
(2) Actinomyces similar to or identical with Walker's organism obtained from human and rat leprosy, or
(3) Stages in the life cycle of true, attenuated mammalian or avian tubercle bacilli, or
(4) Contaminating acid-fast soil saprophytes, or
(5) A new, undescribed species.

We believe that this study has given us a considerable amount of evidence which indicates that they are not *Mycobacterium tuberculosis*. It is our opinion that they will be found to be an undescribed species.

Probably the best, if not the only method, of distinguishing them must be eventually by chemical methods. For this reason, the organisms have been submitted to the Committee on Medical Research of the National Tuberculosis Association and early steps are being taken for their chemical analysis. It is hoped that this will throw some light on this extremely interesting and important problem.

Acknowledgments

Thanks are extended for the valuable aid given by the following: Dr. F. E. Murray, Dr. W. D. Wright and Dr. E. P. Durham of the Bureau of Animal Industry, U. S. Department of Agriculture; Dr. A. J. Webb, sanitary inspector, Ogden, Utah; Dr. D. E. Madsen, Director of the Animal Pathological Laboratory, Utah Agricultural Experiment Station; and Director P. V. Cardon, of the Utah Agricultural Experiment Station.

REFERENCES

(1) Traum, J.: Jour. Am. Vet. Med. Ass., 1916, xlix, n.s. 2 (2), 254.
(2) Traum, J.: Ibid., 1919, lv, n.s. 8 (6), 639.
(3) Traum, J.: Corn. Vet., 1923, xiii, 3, 240.
(4) Beach, B. A., and Hastings, E. G.: Proc. 28th Ann. Meet. U. S. Live Stock San. Assn., 1924, 117.
(5) Carpenter, C. M., and Goldberg, S. A.: Corn. Vet., 1925, xv, 2, 148.
(6) Crawford, A. B.: Jour. Am. Vet. Med. Ass., 1926, lxix, n.s. 22 (5), 579.
(7) Mitchell, C. A.: Ibid., 1928, lxxiii, n.s. 26 (4), 493.
(8) Van Es, L.: Ibid., 1931, lxxviii, n.s. 31 (3), 371.
(9) Traum, J.: Ibid., 1929, lxxiv, n.s. 27 (4), 553.
(10) Traum, J.: Corn. Vet., 1923, xiii, 3, 240.
(11) Hastings, E. G., Beach, B. A., and Thompson, Isabel: Amer. Rev. Tuber., 1930, xxii, 218.
(12) Day, L. E.: Jour. Am. Vet. Med. Ass., 1928, lxxii, n.s. 25 (6), 782.
(13) Van Es, L.: Ibid., 1931, lxxviii, n.s. 31 (3), 371.
(14) Crawford, A. B.: Ibid., 1928, lxxiii, n.s. 26 (2), 216.

(15) ELDER, C., AND LEE, A. M.: Ibid., 1924, lxiv, n.s. 17 (4), 440.
(16) HAGAN, W. A., AND ZEISSIG, A.: Ibid., 1929, lxxiv, n.s. 27 (7), 985.
(17) FUNK AND HUNTOON: Jour. Immunol., 1930, xix, 237.
(18) FELDMAN, W. H.: Corn Vet., 1931, xxi, 268.
(19) DAINES, L. L., AND AUSTIN, H.: Proc. 35th Ann. Meet. U. S. Live Stock San. Assn., 1931, 414.

TUBERCULOSIS DISPENSARY PRACTICE IN NEW HAVEN, CONNECTICUT

H. R. EDWARDS

"Every case of tuberculosis comes from another case," was the slogan of the Early Diagnosis Campaign for 1932. The phraseology only is new, for the principle dates back almost half a century, and was definitely crystallized by Koch's momentous discovery in 1882.

Tuberculosis is primarily a family disease and as such has received considerable close study. Opie (1) studied a series of families in which there was known exposure, and found 80 per cent infection and 30 per cent latent disease, compared to 30 and 10 per cent, respectively, for children in families with no tuberculosis. He concluded that the only sound method of approach was through the family. Chadwick in Massachusetts (2) arrived at similar conclusions. Schlesinger (3) compared 118 London children from tuberculous households with 513 clinically nontuberculous children with no household contact, and found the incidence of infection of the former group 62 per cent and the latter 24 per cent. He concluded that "tuberculosis begets tuberculosis" and the development of infection and disease is directly dependent upon the amount and frequency of the infection. Schram (4) analyzed 500 children from birth to 8 years who had lived in homes where there was a diagnosed case of tuberculosis. Of 268 exposed to positive-sputum cases 69.4 per cent were infected and of 174 exposed to negative-sputum cases only 50 per cent were infected. Pollak (5) found 95.9 per cent infection in a series of 49 infants between 6–12 months of age from homes of the tuberculous. The literature is replete with other examples of a similar character, and the only conclusion to be drawn is the importance and necessity of more active effort to routinely examine each member of a household in which a diagnosed case of tuberculosis is found. The more important families obviously are those with a member with positive sputum. Rathbun (6) states that 50 to 75 per cent of adult tuberculosis develops from 4 per cent of the school population that have had a childhood type of the disease. He analyzed 24 random families in which a child was found to have a childhood-type lesion in the course of his ex-

aminations in the public schools. In 54 per cent a parent had either died of tuberculosis or was ill with the disease at the time, and 17 per cent had suspicious lesions. Eighty-seven per cent of children examined in these families had signs of tuberculous disease.

The importance of a positive tuberculin test in a child as a lead to probable manifest disease in the home or immediate contacts is not clearly understood at this time. A series of 100 families is now under observation in New Haven, and will be reported on later.

The only existing standards for tuberculosis-clinic practice are contained in the Appraisal Form for City Health Work (7). They are concerned primarily with the number of clinic visits, the ratio of visits to individual patients attending, the percentage of incipient diagnoses of the total, and the number of contacts examined per each new positive case registered. This latter item is estimated at three, and is therefore an average.

These facts undoubtedly give a fair representation of the type of work being done, but they are at best only minimum standards. Many cities are surpassing the standards quoted in one or more items. It is fair to say that with a well-organized dispensary we should expect to know more exactly the completeness of examinations of household or other intimate contacts, if we are to adjudge our control activities fairly.

The death-rate from tuberculosis (all forms) in New Haven has dropped from 197.7 per 100,000 in 1900 to 54.7 (corrected) in 1931, a decrease of over 72 per cent. In 1916 our corrected rate was 126.88; thus the 1931 rate represents a decrease of 56 per cent in 15 years. The part played in this decrease by the dispensary cannot be reduced to a known formula, but it undoubtedly has played a vital part in preventing the development of manifest disease among the many contacts that have been under its supervision.

It is of interest then to analyze closely the thoroughness with which the tuberculosis dispensary has approached the problem of tuberculosis in New Haven families. It should be stated in passing that the dispensary is available to nonresidents as well as to residents. The former comprise about 30 per cent of their dispensary rosters, and are not included in the study to follow.

There are approximately 1,500 diagnosed cases of tuberculosis (all forms) on the roster of the Bureau of Tuberculosis of the New Haven Department of Health. These individuals represent 1,308 families; 661 of them have been known to the New Haven Dispensary at some time,

and the great majority are still under dispensary supervision. The remainder, except for about 100 families under the care of private practitioners, are under the supervision of the New Haven Visiting Nurse Association. This Association also supervises all dispensary cases.

The New Haven Dispensary is the outpatient department of the New Haven Hospital and Yale School of Medicine. It is desirable to outline briefly its major policies and methods of procedure to enable the reader to visualize the set-up for supervising tuberculous families.

ORGANIZATION

1: History: The New Haven Dispensary was started in 1870, and has been in continuous operation since. In 1907, due to stimulation from the Gaylord Farm Sanatorium, which was opened in 1904, a special tuberculosis division was created and has been continued since. In 1925 the tuberculosis division was further divided into a pediatrics division for children from 1 to 6 years and a medical division for the age-group 6 and up.

The New Haven Department of Health operated a municipal tuberculosis dispensary between 1920 and 1926. At its close all patients were referred to the New Haven Dispensary.

2: Personnel: In 1926 there was a complete reorganization of tuberculosis activities in New Haven (8). The director of the newly created Bureau of Tuberculosis assumed the responsibilities of that office, the tuberculosis work in the New Haven Hospital and dispensary, and the medical directorship of the William Wirt Winchester Hospital. In 1927 the director resigned the directorship of the Bureau of Tuberculosis to devote full time to the remaining services. The personnel of the tuberculosis clinic fortunately has changed but little since its opening in 1907. The clinician in charge at that time remained until July of 1927, and his successor is still in charge.

The Pediatrics Division was created in 1924 and staffed by the Department of Pediatrics of Yale Medical School. It was organized for purposes of research (9) (10) into the problem of tuberculosis in infancy and early childhood, and is continuing those studies with others at the present time.

The dispensary has an adequate assistant staff. The Medical Division has in attendance, each clinic period, three well-qualified clinicians, and the Pediatrics Division has two. In addition, there are usually three medical students working under the trained staff. This ample staff assures each patient prompt and thorough examination.

The nursing service at the tuberculosis clinic did not become established on a full-time basis until 1921. Previous to that time the New Haven Visiting Nurse Association detailed a nurse from their staff. Since 1921, the adult

division has been fortunate in having the uninterrupted service of the same nurse. The Pediatrics Division has had the full-time service of a nurse since its organization. These nurses make at least one home visit to every new case of tuberculosis admitted, and their long tenure of office assures an intimate knowledge of the social and economic factors in each family under supervision.

The New Haven Visiting Nurse Association carries all families under dispensary supervision and is primarily responsible for the routine home supervision of cases and contacts. Additional nursing service is rendered by the public-school nurses.

3: General Policies: (*A*) *Admission of Cases:* The New Haven Dispensary is open to any case not able to meet the cost of private medical care. The Tuberculosis Divisions are primarily interested in cases with either a diagnosis or suspicion of tuberculosis, and the family contacts. Other divisions of the dispensary, representing the various medical and pediatrics specialities, refer cases with definite or suspicious evidence of pulmonary disease, as well as children with positive tuberculin tests, discovered in the course of routine examinations. Thus the tuberculosis division has built up a large clientele of cases with nontuberculous pulmonary disease, such as bronchiectasis, bronchitis, asthma, pleurisy, pneumonoconiosis, etc. The contact group consists of all individuals having had known contact with a diagnosed case, and all children under 15 who have a positive tuberculin reaction without known family or other source of infection. The latter group is tabulated separately in our monthly reports.

The policy, on examination of contacts to known cases, has always been to examine all members of the family, but not until 1927 has equal emphasis been placed on adults and children. At present an attempt is made to examine all members of the household, nonhousehold and other contacts to a given case, to discover, if possible, the primary source of the disease. The same effort is made in children with a positive tuberculin reaction, who show no manifest disease nor have known contact.

(*B*) *Physical Examination:* Each individual admitted is given a complete chest examination and a more superficial examination of the head and nasopharynx. Should there be evidence of abnormalities in the nasopharynx, eyes, ears, or other parts, the case is referred to the clinic specializing in that particular part for diagnosis and recommendations. Thus every case following advice may be assured of a complete physical examination.

(*C*) *Tuberculin Testing:* In general every child up to 16 years of age, examined in the tuberculosis clinic, is tuberculin-tested. Adults are also tested in selected cases, and more and more this is becoming a routine. Old Tuberculin has been used since the earliest days of the dispensary. Until 1924 the Pirquet test was employed, and since then the Mantoux technique. Our dilutions

of the latter have been equivalent to 0.02-, 0.1- and 1-mgm. doses. Formerly the case was given increased dosage if negative to the lower dilution in the order stated. At present, if a case fails to react to 0.02 mgm., the test is repeated with 1 mgm. O.T. This procedure meets with less objection from the patient, establishes the evidence of infection earlier, and thus far, has shown no unfavorable reactions with the use of 1-mgm. dosages following a negative 0.02 mgm.

All tests are read after 48 hours at the clinic if possible, and, if negative, repeats are made at the visits to the clinic by the nurse or physician. In those cases in which it is not practicable for the patient to return to the clinic the reading is made by the visiting or school nurse, or by the clinic nurse in the course of home visits. Repeat tuberculin tests in this latter group of negative reactors are made at the clinic at subsequent appointments.

The use of tuberculin in the Pediatrics Division is somewhat different than in the Medical Division. There, for purposes of research, they do not immediately increase the dosage for negative reactors, but may carry a case over a period of five years and record as many as 12 or more negative tests to 0.1-mgm. or repeated 1-mgm. dosages. All cases in this division reaching the age of six years are automatically transferred to the Medical Division, where the tuberculin test is carried through 1.0 mgm. If a case fails to react to 1.0 mgm. of O.T. and there is no known case of pulmonary or other open tuberculosis in the family or immediate contacts, the case is discharged. Only in specially selected cases do we continue to carry a child negative to O.T. and contact with a member in the family with calcified mesenteric or apparently calcified tracheobronchial lymph nodes.

(*D*) *X-Rays:* It has been a routine procedure to make roentgenograms of all children reacting to tuberculin, and occasionally of nonreactors, if there is a question of pulmonary disease. All adults with evidence of intrapulmonary disease are likewise roentgenographed. Repeat examinations are made at periodic intervals, depending upon the individual case, of all cases with manifest disease. For children the following combinations are usually made at the outset: Stereo of the chest and P.A. of the abdomen. The chest exposure may be varied by a single P.A. and oblique. If there is suggestive evidence in the cervical lymph nodes, a P.A. is made of the neck.

(*E*) *Consultation Cases:* The dispensary offers a diagnostic service to physicians wishing to refer their cases. Such cases, when completed, are referred back to their family physicians for treatment and supervision, and a complete report of the dispensary findings and recommendations is sent to the physician. This service is not utilized as it might be by the private practitioners.

(*F*) *Records:* The unit form of record-keeping is used, all notes being made in narrative form. Each case-folder contains records of all examinations, diagnoses, recommendations and treatments for that case both in the dispen-

sary and in the New Haven Hospital. In addition, a social-service record is kept in each folder of pertinent family and social data, reports from and to physicians, visiting nurse, sanatoria, and hospitals.

Since November, 1931, family folders have been set up for each family listing the household and nonhousehold family and other contacts. Each individual's age, date of admission to the dispensary, results of tuberculin tests and X-ray examination, and diagnoses are entered; also the deaths and the sanatorium or hospital experience among those listed. Thus we have a complete picture of the tuberculosis problem in each family and can with facility direct our energies to the most needful factor. After all available data are recorded on these charts, a conference is arranged with the dispensary nurses, the tuberculosis supervisor of the Visiting Nurse Association, and the Director of the Bureau of Tuberculosis of the New Haven Department of Health. Each family is then reviewed as a unit, and suggestions made for specific action. As a result, about 50 new family contacts were cleared in a single month. It is also possible from this type of set-up to eliminate from nursing service individuals or families no longer requiring supervision, a great saving of nursing time and service.

(*G*) *Laboratory Examinations:* Every case raising sputum is requested to submit specimens for examination in suitable containers provided. If five direct smears are negative for tubercle bacilli, examination of concentrates is ordered, or the specimen may be cultured or inoculated into guinea pigs. If indicated, studies for fungi or other microörganisms are made. All other examinations, such as blood, urine, etc., are secured through the general medical or pediatrics clinics.

(*H*) *Period of Supervision of Cases:* All adults with manifest disease are carried until they enter sanatoria, leave town or die, unless they put themselves under the care of a private practitioner. Those returning from sanatoria, or reëstablishing their residence in the city are readmitted. There are a few patients with well-healed minimal lesions who are discharged after a period of observation sufficient to assure the complete healing of their disease. Essentially the same procedure is followed with children. Also an effort is made to keep under supervision all those children who react to tuberculin, and have no manifest disease, until they reach the age of 25 years. It is hoped that in time this method will add something of value to our knowledge of the pathogenesis of the disease.

AN ANALYSIS OF 661 TUBERCULOUS FAMILIES UNDER SUPERVISION AT THE NEW HAVEN DISPENSARY

The data for this analysis were secured from the family charts previously mentioned.

The families studied date back to first diagnoses made in 1910, or earlier, and represent all new admissions up to May 1, 1932. As stated previously, equal emphasis on examinations of adults and children is a matter of recent practice. Thus the total adults cleared are naturally lower than will be the experience from now on. Likewise, the more recently admitted families have not been under supervision long enough to permit examination of all family contacts.

For convenience of handling the data, each family has been divided into adults and children on the basis of the first diagnosis of manifest disease in the family. Those members over 15 years of age at that time are classified as adults, and those 15 years or under as children.

Examinations

A general summary of the total families and individuals examined is given in table 1.

TABLE 1

Examinations of individuals in 661 families

	INDIVIDUALS		PER CENT EXAMINED
	Number represented	Number examined	
Male	1,911	1,267	66.3
Female	1,945	1,422	73.1
Adults	1,907	1,142	59.8
Children	1,949	1,551	79.5
Total	3,856	2,693	69.8

In 1929 Korns (10) reported that (excluding Gowanda Village and tribal Indians over whom he had no supervision) there were 1,225 household contacts to the 654 diagnosed cases on his roster in Cattaraugus County. Five hundred and seventy-five, or 47 per cent, of these contacts had been examined as of December 31, 1929. In 1931 there were 396 contacts under 20 years, 288, or 73.0 per cent, of whom were examined. There were 429 contacts over 20 years and 253, or 59.0 per cent, examined. Of the total 825 contacts, 541, or 66 per cent, were examined by December 31, 1931.

How nearly the Cattaraugus County experience represents the practice in other communities is not known, as similar reports have not been seen by the writer. A very intensive tuberculosis-control program has

been in operation in Cattaraugus County since 1921 (13), and we may expect a higher percentage of contact examination than in the average community. It must also be obvious that a similar campaign has been under way in New Haven to have cleared 69.8 per cent of all individuals exposed to the originally diagnosed case in the family.

Our records show that in 258 families all members have been examined, and in 395 families all members available have been examined. In many instances, especially among the families admitted 10 or more years ago, many of the members have been married and are now living away from New Haven.

In 545 families our first diagnosis was of pulmonary tuberculosis and in 116 some other form, chiefly a childhood type or lymphatic disease (cervical or mesenteric lymphadenitis). In the former the father was diagnosed first in 226 instances, the mother in 170, a child in 121, and other nonfamily members in 28. There were 53 families in which the first knowledge of pulmonary tuberculosis was secured from a death-certificate. For the most part these individuals had been diagnosed before death, several in local hospitals, but had not been reported to the health-officer as required by law.

It will be of interest to note the completeness of examinations of members of families in which our first diagnosis was of pulmonary tuberculosis (table 2). It is clear from this tabulation that the greatest emphasis has been placed on the most infectious cases.

There was a group of four families in which the first diagnosed case was miliary tuberculosis or tuberculous meningitis. There were 28 individuals in contact and 24, or 85.7 per cent, have been examined (66.6 per cent of the adults and 94.7 per cent of the children).

TABLE 2

A classification of individuals examined, based on those families (545) in which the first diagnosis was of pulmonary tuberculosis

	INDIVIDUALS		PER CENT EXAMINED
	Number represented	Number examined	
Male	1,569	1,087	69.2
Female	1,607	1,218	75.7
Adults	1,636	1,050	64.1
Children	1,540	1,259	81.7
Total	3,176	2,309	72.7

Sputum Examinations

The number of individuals with positive sputum are indicated in table 3. Thus, 323 of the 762 cases diagnosed as pulmonary tuberculosis are known to have been open cases at some time. If the results of sputum examinations in State sanatoria prior to 1916 were available, this number would be increased, and without doubt the 53 individuals in which the first knowledge of tuberculosis was known by a death-certificate had bacilli in their sputa.

TABLE 3

Sputa showing tubercle bacilli

	SPUTA SHOWING TUBERCLE BACILLI
Male	200
Female	123
Adults	292
Children	31
Total	323

Tuberculin Testing

The use of tuberculin for diagnostic purposes was not as generally used in the earlier years of the tuberculosis dispensary as it has been since 1925. Nevertheless, 76.9 per cent of our children have had a tuberculin test, and several of those reported negative have had as high as 12 or more tests. It is our policy not to consider a test negative until the patient has had at least one injection of 1.0 mgm., and not infrequently we repeat this amount. The use of tuberculin is shown in table 4.

TABLE 4

Results of tuberculin testing in 661 families

	TOTAL	TOTAL TUBERCULIN TESTED	TOTAL REACTING TO TUBERCULIN	PERCENTAGE REACTING TO TUBERCULIN
Adults	1,142	166	156	94.5
Children	1,551	1,193	803	67.3
Total	2,693	1,359	959	70.5

Use of X-Ray

We have been very fortunate in the X-ray facilities provided, especially considering the fact that our routine requires an initial three films of each child. In numerous instances we have series of 6 to 12 exposures, and even more. In brief, we repeat X-rays whenever the condition of the case requires it. The extent to which X-rays have been utilized in the 661 families studied is indicated in table 5. Routine roentgenograms in adults are not ordinarily made if the history and physical examination fail to reveal suspicious or definite evidence of change in the lungs.

TABLE 5

The use of X-rays in the 2,693 individuals examined

AGE	TOTAL EXAMINED	TOTAL X-RAYED	PER CENT X-RAYED
Adults	1,907	684	35.8
Children	1,949	979	50.2
Total	3,856	1,663	42.8

DIAGNOSES MADE

In the 2,693 individuals examined 1,258 diagnoses of tuberculous disease in some form were made. Six hundred and sixty-one were the original diagnoses. Thus 597 new diagnoses of tuberculosis were made, or an average of 0.9 new cases. It is reasonable to suppose that if all members of families were examined this average would be higher. In the 545 families in which the first diagnosis was pulmonary tuberculosis there were found 211 new cases of pulmonary tuberculosis, whereas in the 116 families in which the first case was a nonpulmonary form of tuberculosis, there were found only 6 cases of pulmonary tuberculosis. This again emphasizes the importance of pulmonary tuberculosis in the pathogenesis of the disease. The diagnoses in the 2,693 individuals are indicated in table 6.

TABLE 6

Diagnoses made in examination of 2,693 individuals

	TOTAL	PER CENT OF TOTAL	ADULTS	CHILDREN
Pulmonary tuberculosis, adult type	762	28.36	633	129
Childhood-type tuberculosis	324	12.03	52	272
Lymph-node (cervical and mesenteric)	103	3.83	9	94
Bone	15	0.55	3	12
Meningitis, pleurisy, etc	54	2.00	20	34
No manifest disease	786	29.18	135	651
Nontuberculous	520	19.30	265	255
Deferred	129	4.79	25	104
Total	2,693	100.00	1,142	1,551

There were 81 families in which the first diagnosis was of a childhood form, or lymphatic disease (cervical or mesenteric lymphadenitis). There were 407 individuals represented, 222, or 54.5 per cent, of which were examined. In this group we found only *one* case of pulmonary tuberculosis, adult form, 44 of childhood type, and 42 of cervical or mesenteric lymphadenitis. This total of 87 diagnoses of tuberculous disease constitutes 39 per cent of those examined. Of the 248 classed as children, 173, or 69.7 per cent, were examined, and 73, or 42 per cent, had evidence of tuberculous disease. This latter figure is apparently much lower than Rathbun's (6) finding of 87 per cent of children with "signs of tuberculous disease" in 24 families in which all members were examined.

CHANGES IN DIAGNOSES

A measure of the effectiveness of constant supervision of members of the families in this study may be obtained from a perusal of the changes made in diagnoses during the period under observation, as shown in table 7. In 15 instances a less serious diagnosis, such as questionable pulmonary, childhood, lymph-node, or other form was changed into that of a pulmonary lesion. Four were detected in a minimal stage, three of which were classified as arrested or quiescent. Eleven developed into moderately or far-advanced disease; of this latter group four are now dead, seven have had hospital care and two are still in the sanatorium.

TABLE 7

Changes in original diagnoses of 2,693 examinations

ORIGINAL DIAGNOSIS	CHANGED TO	NUMBER
Pulmonary tuberculosis	Nontuberculous	24
Pulmonary tuberculosis	Childhood type	7
Pulmonary tuberculosis	Healed pleurisy	1
Pulmonary tuberculosis	Bone	1
Pulmonary tuberculosis	Lymph-node cervical or mesenteric	1
Pulmonary tuberculosis questionable	Nontuberculous	1
Pulmonary tuberculosis questionable	Pulmonary tuberculosis	1
Childhood-type tuberculosis	Nontuberculous	7
Childhood-type tuberculosis	Pulmonary tuberculosis	3
Childhood-type tuberculosis	Lymph-node tuberculosis	1
Lymph-node tuberculosis, cervical or mesenteric	Nontuberculous	6

TABLE 7—*Concluded*

ORIGINAL DIAGNOSIS	CHANGED TO	NUMBER
Lymph-node tuberculosis, cervical or mesenteric	Pulmonary tuberculosis	3
Lymph-node tuberculosis, cervical or mesenteric	Childhood type	9
Phlyctenular disease	Nontuberculous	4
Phlyctenular disease	Childhood type	14
Phlyctenular disease	Lymph-node tuberculosis	2
Pleurisy	Pulmonary tuberculosis	3
Nontuberculous	Pulmonary tuberculosis	6
Nontuberculous	Childhood type	5
Nontuberculous	Lymph-node tuberculosis	4
Nontuberculous	Phlyctenular	2
		Total: 105

HOSPITALIZATION

Early hospitalization for tuberculosis cases has been a practice in New Haven for several years. Although the waiting time for the State sanatoria has been from 4 to 6 months, it has been possible to finance temporary care in local hospitals and sanatoria pending vacancies in the State sanatoria. The Appraisal Form Standards (7) require 25,000 patient days per 100 deaths, and our performance has been as indicated in table 8.

TABLE 8

Hospitalization of tuberculosis cases by New Haven, 1928–1931

YEAR	RESIDENT DEATHS	HOSPITALIZATION (PATIENT DAYS)	
		Required A. P. H. A. standard	Accomplished
1928	119	29,750	69,945
1929	95	23,750	78,110
1930	93	23,250	76,337
1931	89	22,250	79,107

The National Tuberculosis Association has advocated a ratio of one case hospitalized for each annual death until the past year, when the ratio was raised to two cases for each annual death. In New Haven, this 2 to 1 ratio has been exceeded since 1928. In 1931 there was an average of 199 New Haven residents hospitalized for tuberculosis each month of the year. This is 21 cases in excess of the ratio, and, had more beds been available, the average would have been still higher. The average

length of residence for all patients discharged from sanatoria was: 1928, 191.5 days; 1929, 378.6 days; 1930, 303.0 days; and 1931, 256.1 days.

The hospitalization of individuals in the group under discussion is indicated in table 9. For the most part this hospitalization was rendered to the diagnosed cases.

TABLE 9

Hospitalization of 631 individuals of the 2,693 examined

AGE	TOTAL DIAGNOSED	TOTAL HOSPITALIZED ONE OR MORE TIMES	PER CENT HOSPITALIZED
Adults	1,142	443	38.7
Children	1,551	188	12.1
Total	2,693	631	23.4

New Haven has had summer-camp facilities for contact children since 1912. Until 1926 the camp was operated as a day camp. Since then it has been a 24-hour camp for three months in the summer, and, in all essentials, is comparable to a preventorium. The average enrollment for the past few years has been from 80 to 100 children, all of whom react positively to tuberculin, while many have an inactive childhood or lymph-node disease. This period of rehabilitation, short as it is, has been instrumental in preventing in these children the lowered resistance so frequently followed by a spread of their disease process.

DEATHS

The deaths occurring in this group of families are indicated in table 10.

TABLE 10

Deaths occurring in 661 families on or after first diagnosis was made

TYPE OF DEATH	TOTAL	ADULTS	CHILDREN
Tuberculosis deaths in family or immediate contacts	361	261	45
Deaths from other causes occurring after first diagnosis	64	29	35
Total	425	290	80

SUMMARY

New Haven has had a special tuberculosis dispensary service since 1907. In 1925, the service was divided into an adult and a child division. Emphasis has been placed on the family as a unit from the outset,

with more attention to the child contacts until 1927, since when equal emphasis has been placed on adults to discover the possible original source of infection in the family.

A group of 661 families is presented, covering admissions to the dispensary since 1910, and more especially those admitted since 1920. There have been at some time 3,856 individuals in these families exposed to the originally diagnosed case. Of this total there have been examined 2,693, or 69.8 per cent,—59.8 per cent of the adults and 79.5 per cent of those classed as children (15 years or under at the time of first diagnosis in the family). In 545 families in which the first diagnosis was of pulmonary tuberculosis 72.7 per cent of all family members were examined, —64.1 per cent of the adults and 81.7 per cent of the children.

There were made 1,258 diagnoses of tuberculous disease, comprising the original diagnosis (661) in the family and 597 new diagnoses. Two hundred and eleven new diagnoses of pulmonary tuberculosis were made in the 545 families in which the first diagnosis was pulmonary tuberculosis, and only one diagnosis of pulmonary tuberculosis when the first diagnosis in the family was of childhood or lymph-node disease. Of the total examined (2,693), including the original diagnosis, 46.7 per cent were found to have evidence of manifest tuberculous disease.

Fifteen of the 597 discovered new cases have developed adult pulmonary disease from a less serious lesion. This indicates the value of constant supervision of all cases with manifest disease, and of positive tuberculin cases without manifest disease at the time of first examination.

Our findings indicate conclusively the importance of handling tuberculosis from the standpoint of the family if we are to effect adequate control and prevention.

REFERENCES

(1) Opie, E. L.: Jour. Outdoor Life, 1927, xxiv, 274.
(2) Chadwick, H. D.: Amer. Rev. Tuberc., 1928, xvii, 318.
(3) Schlesinger, B., and Hart, D. A.: Arch. Dis. Child., 1930, v, 191.
(4) Schram, T.: Tubercle, 1922, iii, 529.
(5) Pollak: Beitr. z. Klin. d. Tuberc., 1911, xix, 469.
(6) Rathbun, W. L.: Tr. Nat. Tuberc. Ass., 1929, xxv, 278.
(7) Appraisal Form for City Health Work, Am. Pub. Health Ass., 1929.
(8) Edwards, H. R.: Amer. Rev. Tuberc., 1930, xxi, 233.
(9) Dunham, E. C., and Smythe, A. M.: Am. Jour. Dis. Child., 1927, xxxiv, 962.
(10) Dunham, E. C., and Smythe, A. M.: Ibid., 1926, xxxi, 815.
(11) Aronson, J. D.: Am. Jour. Hygiene, 1931, xiv, 374.
(12) Korns, J. H.: Unpublished reports of Bureau of Tuberculosis, Cattaraugus County Department of Health, 1929 & 1931.
(13) Winslow, C.-E. A.: Health on the farm and in the village, The MacMillan Co., 1931.

INDEX OF SUBJECTS AND AUTHORS

Abdominal symptoms, acute, Spontaneous pneumothorax with, 67

Abscesses, pulmonary, pyogenic, Comparison of pathological changes in embolic tuberculous and, 150

Activity in pulmonary tuberculosis, current conception of, Protest against, 101

Acute abdominal symptoms, Spontaneous pneumothorax with, 67

Adherent tuberculous cavities, Closure of, by combined artificial pneumothorax and phrenicectomy, 355

Adult primary tuberculous infection, Tendencies in. II. Studies on the pathogenesis of primary tuberculous infection, 575

Alcohol and tuberculosis, 217

Allergy and anaphylaxis to tuberculoprotein, Sensitization of guinea pigs and production of, 291

ALPERT, LOUIS. The sanatorium treatment of lupus, 515

Altitude, climate and, Change of. I. Its effects on tuberculosis patients, 247

American Negro and white race, Pathological anatomy of pulmonary tuberculosis in, 411

Anaphylaxis, allergy and, to tuberculoprotein, Sensitization of guinea pigs and production of, 291

Anatomy, Pathological, of pulmonary tuberculosis in American Negro and white race, 411

Aneurysm, aortic, and pulmonary fibrosis, Spontaneous pneumothorax with, 553

Animals, experimental, Pulmonary roentgenography of small, 137

—— of varying resistance, Comparison of tissue reactions to pulmonary infection with tubercle bacilli in, 270

Aortic aneurysm and pulmonary fibrosis, Spontaneous pneumothorax with, 553

Appliance for immobilization in pulmonary tuberculosis, 375

ARONSON, JOSEPH D., ZACKS, DAVID, AND POUTAS, J. J. The comparative sensitiveness of the Pirquet and the intracutaneous tuberculin tests, 465

Artificial pneumothorax and phrenicectomy, combined, Closure of adherent tuberculous cavities by, 355

—— —— technique, Some aspects of, 522

Attenuation of *BCG*, Fixity of, 1

AUSTIN, HAROLD, AND DAINES, LYMAN L. A study of so-called skin lesions of tuberculin-reacting cattle, 600

Bacilli, tubercle, Comparison of tissue reactions to pulmonary infection with, in animals of varying resistance, 270

——, ——, cultivation of, from sputum, Comparison of certain media for, 259

BANYAI, ANDREW L., AND GRILL, JOHN. So called pleuropulmonary endothelioma, 193

BARACH, ALVAN L. The use of filtered-air chambers in pulmonary tuberculosis, 508

BCG, attenuation of, Fixity of, 1

——, Protection against tuberculosis with, in guinea pigs, 6

Benign pulmonary tuberculosis with diabetes, 47

BIRKHAUG, KONRAD E. Protection against tuberculosis with *BCG* in guinea pigs, 6

BLOCH, ROBERT G. Localized experimental tuberculosis of the lungs, 143

Blood counts in 150 clinical cases of tuberculosis and underlying pathological changes as shown by serial X-ray films, Correlation of, 488

—— differential count, Schilling, Tuberculin and, in diagnosis and classification of tuberculosis, 377

—— pressure in tuberculosis, 342

BOISSEVAIN, C. H. The production of tuberculous tissue and hypersensitiveness to tuberculin in guinea pigs, 595

BOMMER, S. The dietary treatment of skin tuberculosis, 209
BOOK REVIEWS: *Exploration radiologique de l'appareil respiratoire*—Sergent, Bordet & Durand, 108; *Die Lungentuberkulose, Lehrbuch der diagnostischen Irrtümer*—Nico & Schroeder, 109; *Die Perkussion der Lungenspitzen*—Winkler, 111; *Über die neuere Entwicklung der chirurgischen Behandlung der Lungentuberkulose*—Nissen, 111; *Ernährung und Diät bei Tuberkulose*—Rehfeldt, 113; *Vaccination preventive de la tuberculose de l'homme et des animaux par le BCG*, 115; *Die Prognose der offenen Lungen-Tuberkulose bei Kindern und Jugendlichen*—Klare, 117; *Tuberkulose als Schicksal*—Ebstein, 118. (All reviews by MAX PINNER.)
Brain, Tuberculoma of, 171
Bredeck, J. F. Tuberculin and Schilling blood differential count in diagnosis and classification of tuberculosis, 377
BROWN, LAWRASON, AND EAGAN, JOSEPH T. Alcohol and tuberculosis, 217

CALMETTE, A. The fixity of the attenuation of *BCG*, 1
Case-finding, tuberculosis, Fluoroscopy, 71
Cattle, tuberculin-reacting, skin lesions, Study of so-called, 600
Cavities, tuberculous, adherent, Closure of, by combined artificial pneumothorax and phrenicectomy, 355
Change of climate and altitude. I. Its effects on tuberculosis patients, 247
Classification of tuberculosis, Tuberculin and Schilling blood differential count in diagnosis and, 377
Climate and altitude, Change of. I. Its effects on tuberculosis patients, 247
Closure of adherent tuberculous cavities by combined artificial pneumothorax and phrenicectomy, 355
Codliver-oil concentrate injections, Effects of, 368
COHEN, SEYMOUR J. The gastric function in tuberculosis, 330.
Combined artificial pneumothorax and phrenicectomy, Closure of adherent tuberculous cavities by, 355
Comparative sensitiveness of Pirquet and intracutaneous tuberculin tests, 465
Comparison of certain media for cultivation of tubercle bacilli from sputum, 259
—— —— pathological changes in embolic tuberculous and pyogenic pulmonary abscesses, 150
—— —— tissue reactions to pulmonary infection with bacilli in animals of varying resistance, 270
Congenital cystic disease of lung, 59
Consulting service for roentgenologists, Engineering, 216
Correlation of blood counts in 150 clinical cases of tuberculosis and underlying pathological changes as shown by serial X-ray films, 488
Costa and red-cell sedimentation reactions in laryngeal tuberculosis, 92
Count, Schilling blood differential, Tuberculin and, in diagnosis and classification of tuberculosis, 377
Counts, blood, in 150 clinical cases of tuberculosis and underlying pathological changes as shown by serial X-ray films, Correlation of, 488
Cultivation of tubercle bacilli from sputum, Comparison of certain media for, 259
Current conception of activity in pulmonary tuberculosis, Protest against, 101
CUTLER, J. W. Some aspects of artificial-pneumothorax technique, 522
Cystic disease of lung, Congenital, 59

DAINES, LYMAN L., AND AUSTIN, HAROLD. A study of so-called skin lesions of tuberculin-reacting cattle, 600
DAVIS, ELIZABETH A., AND SHIPMAN, SIDNEY J. Tuberculosis and tuberculous infection among nurses, 474
DAVIS, S. C. An appliance for immobilization in pulmonary tuberculosis, 375
Developments in our knowledge of tuberculosis, Recent, 121
Diabetes, Benign pulmonary tuberculosis with, 47
Diagnosis and classification of tuberculosis, Tuberculin and Schilling blood differential count in, 377
Dietary treatment of skin tuberculosis, 209

Differential count, Schilling blood, Tuberculin and, in diagnosis and classification of tuberculosis, 377
Disease, cystic, of lung, Congenital, 59
Dispensary, Tuberculosis, practice in New Haven, Connecticut, 611
DONALDSON, LILIAN C., AND VORWALD, ARTHUR J. The effect of tuberculin on spermatozoa from normal and tuberculous guinea pigs, 401

EAGAN, JOSEPH T., AND BROWN, LAWRASON. Alcohol and tuberculosis, 217
EDWARDS, H. R. Tuberculosis dispensary practice in New Haven, Connecticut, 611
Effect of tuberculin on spermatozoa from normal and tuberculous guinea pigs, 401
Effects of codliver-oil concentrate injections, 368
—— —— thoracoplasty on heart, 200
Embolic tuberculous and pyogenic pulmonary abscesses, Comparison of pathological changes in, 150
Emotion in tuberculosis, Rôle of, 315
Endothelioma, pleuropulmonary, So called, 193
Engineering consulting service for roentgenologists, 216
EVERETT, FRANKLIN R. Pathological anatomy of pulmonary tuberculosis in American Negro and white race, 411
Experimental animals, Pulmonary roentgenography of small, 137
—— tuberculosis of lungs, Localized, 143
EYRE, MARY B. The rôle of emotion in tuberculosis, 315

FALES, LOUIS H. A protest against the current conception of activity in pulmonary tuberculosis, 101
Female genital tract, tuberculous infection of, Study of, 589
FERRIS, HENRY W. Generalized tuberculosis complicated by presence of yeast-like organisms, 348
Fibrosis, pulmonary, Spontaneous pneumothorax with aortic aneurysm and, 553
Filtered-air chambers in pulmonary tuberculosis, Use of, 508
Fixity of attenuation of *BCG*, 1
FLAHIFF, E. W., AND HETHERINGTON, H. W. Fluoroscopy in tuberculosis case-finding, 71
FLINN, JOHN W., ROBERT S., AND ZEBUD M. The correlation of blood counts in 150 clinical cases of tuberculosis and underlying pathological changes as shown by serial X-ray films, 488
Fluoroscopy in tuberculosis case-finding, 71
Function, Gastric, in pulmonary tuberculosis, 330

Gastric function in pulmonary tuberculosis, 330
Generalized tuberculosis complicated by presence of yeast-like organisms, 348
Genital tract, female, tuberculous infection of, Study of, 589
GOLDBLATT, HARRY, AND REICHLE, H. S. The sensitization of guinea pigs and production of allergy and anaphylaxis to tuberculoprotein, 291
GORDON, BURGESS, AND TITHERINGTON, R. J. The effects of codliver-oil concentrate injections, 368
GRAVES, GRANT O., AND SCOTT, ERNEST. Tuberculoma of the brain, 171
GREENBERG, SIDNEY. Pulmonary roentgenography of small experimental animals, 137
GRILL, JOHN, AND BANYAI, ANDREW L. So called pleuropulmonary tuberculoma, 193
Guinea pigs, Effect of tuberculin on spermatozoa from normal and tuberculous, 401
—— ——, Production of tuberculous tissue and hypersensitiveness to tuberculin in, 595
—— ——, Protection against tuberculosis with *BCG* in, 6
—— ——, Sensitization of, and production of allergy and anaphylaxis to tuberculoprotein, 291

HANSEN, OLGA S., AND MALY, HENRY W. The effects of thoracoplasty on the heart, 200
Heart, Effects of thoracoplasty on, 200
HENNELL, HERMAN, AND WESSLER, H. Benign pulmonary tuberculosis with diabetes, 47

HETHERINGTON, H. W., AND FLAHIFF, E. W. Fluoroscopy in tuberculosis case-finding, 71
Hypersensitiveness to tuberculin in guinea pigs, Production of tuberculous tissue and, 595

Immobilization in pulmonary tuberculosis, Appliance for, 375
Infection, pulmonary, with tubercle bacilli, Comparison of tissue reactions to, in animals of varying resistance, 270
——, tuberculous, by way of female genital tract, Study of, 589
——, ——, primary, pathogenesis of, Studies on. I. The regressive lesions, 559
——, ——, ——, —— ——, —— ——. II. Tendencies in adult primary tuberculous infection, 575
——, ——, Tuberculosis and, among nurses, 474
Intracutaneous, Pirquet and, tuberculin tests, Comparative sensitiveness of, 465

JAFFÉ, R. H. Tuberculosis and leukaemia, 32
JAMESON, EDWIN M. A study of tuberculous infection by way of the female genital tract, 589

KETTERER, G. H. Spontaneous pneumothorax with aortic aneurysm and pulmonary fibrosis, 553
Knowledge of tuberculosis, Recent developments in our, 121
Koch, Preventive and therapeutic measures in tuberculosis since, 529

Laryngeal tuberculosis, Costa and red-cell sedimentation reactions in, 92
Leukaemia, Tuberculosis and, 32
Localized experimental tuberculosis of lungs, 143
Lung, cystic disease of, Congenital, 59
Lungs, tuberculosis of, experimental, Localized, 143
Lupus, treatment of, Sanatorium, 515

MALY, HENRY W., AND HANSEN, OLGA S. The effects of thoracoplasty on the heart, 200
MARVIN, HORACE P., AND POLLOCK, WILLIAM C. Congenital cystic disease of lung, 59
MASTEN, A. R. The blood-pressure in tuberculosis, 342
MAYER, EDGAR. Preventive and therapeutic measures in tuberculosis since Koch, 529
Media for cultivation of tubercle bacilli from sputum, Comparison of certain, 259
Method of recording roentgen-ray readings, 311
MYERS, J. ARTHUR. Recent developments in our knowledge of tuberculosis, 121

Negro, American, and white race, Pathological anatomy of pulmonary tuberculosis in, 411
Normal and tuberculous guinea pigs, Effect of tuberculin on spermatozoa from, 401
Nurse, trained, tuberculosis, The, 81

OECHSLI, WALDO R., AND SKILLEN, JANE. Spontaneous pneumothorax with acute abdominal symptoms, 67
Organisms, yeast-like, Generalized tuberculosis complicated by presence of, 348

Pathogenesis of primary tuberculous infection, Studies on. I. The regressive lesions, 559
—— —— —— —— ——, —— ——. II. Tendencies in adult primary tuberculous infection, 575
Pathological anatomy of pulmonary tuberculosis in American Negro and white race, 411
—— changes in embolic tuberculous and pyogenic pulmonary abscesses, Comparison of, 150
—— ——, underlying, as shown by serial X-ray films, Correlation of blood counts in 150 clinical cases of tuberculosis and, 488
Patients, tuberculosis, Effects of change of climate and altitude on, 247
PHILLIPS, E. W. Change of climate and altitude. I. Its effects on tuberculosis patients, 247
Phrenicectomy, combined artificial pneumothorax and, Closure of adherent tuberculous cavities by, 355

PIERSON, PHILIP H. A comparison of the pathological changes in embolic tuberculous and pyogenic pulmonary tuberculous abscesses, 150
PIRKLE, H. B. A method of recording roentgen-ray readings, 311
Pirquet and intracutaneous tuberculin tests, Comparative sensitiveness of, 465
Pleuropulmonary endothelioma, So called, 193
Pneumothorax, artificial, and phrenicectomy, combined, Closure of adherent tuberculous cavities by, 355
——, ——, technique, Some aspects of, 522
——, Spontaneous, with acute abdominal symptoms, 67
——, ——, —— aortic aneurysm and pulmonary fibrosis, 553
POLLOCK, WILLIAM C., AND MARVIN, HORACE P. Congenital cystic disease of lung, 59
POUTAS, J. J., ARONSON, JOSEPH D., AND ZACKS, DAVID. The comparative sensitiveness of the Pirquet and the intracutaneous tuberculin tests, 465
Practice, Tuberculosis dispensary, in New Haven, Connecticut, 611
Preventive and therapeutic measures in tuberculosis since Koch, 529
Primary tuberculous infection, pathogenesis of, Studies on. I. The regressive lesions, 559
—— —— ——, —— ——, —— ——. II. Tendencies in adult primary tuberculous infection, 575
Production of allergy and anaphylaxis to tuberculoprotein, Sensitization of guinea pigs and, 291
—— —— tuberculous tissue and hypersensitiveness to tuberculin in guinea pigs, 595
Protection against tuberculosis with *BCG* in guinea pigs, 6
Protest against current conception of activity in pulmonary tuberculosis, 101
Pulmonary abscesses, pyogenic, Comparison of pathological changes in embolic tuberculous and, 150
—— fibrosis, Spontaneous pneumothorax with aortic aneurysm and, 553
Pulmonary infection with tubercle bacilli, Comparison of tissue reactions to, in animals of varying resistance, 270
—— roentgenography of small experimental animals, 137
—— tuberculosis, activity in, current conception of, Protest against, 101
—— ——, Benign, with diabetes, 47
—— ——, filtered-air chambers in, Use of, 508
—— ——, Gastric function in, 330
—— ——, immobilization in, Appliance for, 375
—— —— in American Negro and white race, Pathological anatomy of, 411
Pyogenic pulmonary abscesses, Comparison of pathological changes in embolic tuberculous and, 150

Race, white, Pathological anatomy of pulmonary tuberculosis in American Negro and, 411
Reactions, Costa and red-cell sedimentation, in laryngeal tuberculosis, 92
——, tissue, to pulmonary infection with tubercle bacilli in animals of varying resistance, Comparison of, 270
Recent developments in our knowledge of tuberculosis, 121
Recording roentgen-ray readings, Method of, 311
Red-cell sedimentation, Costa and, reactions in laryngeal tuberculosis, 92
Regressive lesions. Studies on pathogenesis of primary tuberculous infection. I, 559
REICHLE, H. S., AND GOLDBLATT, HARRY. The sensitization of guinea pigs and the production of allergy and anaphylaxis to tuberculoprotein, 291
Resistance, varying, animals of, Comparison of tissue reactions to pulmonary infection with tubercle bacilli in, 270
Roentgenography, Pulmonary, of small experimental animals, 137
Roentgenologists, Engineering consulting service for, 216
Roentgen-ray readings, Method of recording, 311
Rôle of emotion in tuberculosis, 315

RUBENSTEIN, CHARLES L. The Costa and red-cell sedimentation reactions in laryngeal tuberculosis, 92

Sanatorium treatment of lupus, 515
Schilling blood differential count, Tuberculin and, in diagnosis and classification of tuberculosis, 377
SCOTT, ERNEST, AND GRAVES, GRANT O. Tuberculoma of the brain, 171
Sedimentation, red-cell, Costa and, reactions in laryngeal tuberculosis, 92
Sensitiveness, Comparative, of Pirquet and intracutaneous tuberculin tests, 465
Sensitization of guinea pigs and production of allergy and anaphylaxis to tuberculoprotein, 291
Serial X-ray films, Correlation of blood counts in 150 clinical cases of tuberculosis and underlying pathological changes as shown by, 488
SHAFFER, M. A comparison of certain media for the cultivation of tubercle bacilli from sputum, 259
SHIPMAN, SIDNEY J., AND DAVIS, ELIZABETH A. Tuberculosis and tuberculous infection among nurses, 474
SKILLEN, JANE, AND OECHSLI, WALDO R. Spontaneous pneumothorax with acute abdominal symptoms, 67
Skin lesions of tuberculin-reacting cattle, Study of so-called, 600
—— tuberculosis, treatment of, Dietary, 209
SLAVIN, PAUL. Closure of adherent tuberculous cavities by combined artificial pneumothorax and phrenicectomy, 355
Small experimental animals, Pulmonary roentgenography, 137
So called pleuropulmonary endothelioma, 193
Spermatozoa from normal and tuberculous guinea pigs, Effect of tuberculin on, 401
Spontaneous pneumothorax with acute abdominal symptoms, 67
—— —— —— aortic aneurysm and pulmonary fibrosis, 553
Sputum, cultivation of tubercle bacilli from, Comparison of certain media for, 259
SWEANY, HENRY C. Studies on the pathogenesis of primary tuberculous infection. I. The regressive lesions, 559
SWEANY, HENRY C. Studies on the pathogenesis of primary tuberculous infection. II. Tendencies in adult primary tuberculous infection, 575
Symptoms, abdominal, acute, Spontaneous pneumothorax with, 67

Tape test with tuberculin ointment, 308
Technique, artificial-pneumothorax, Some aspects of, 522
Test, Tape, with tuberculin ointment, 308
Tests, tuberculin, Pirquet and intracutaneous, Comparative sensitiveness of, 465
Therapeutic measures in tuberculosis since Koch, Preventive and, 529
Thoracoplasty, Effects of, on heart, 200
Tissue reactions to pulmonary infection with tubercle bacilli in animals of varying resistance, Comparison of, 270
——, tuberculous, and hypersensitiveness to tuberculin in guinea pigs, Production of, 595
TITHERINGTON, R. J., AND GORDON, BURGESS. The effects of codliver-oil concentrate injections, 368
Trained nurse, tuberculosis, The, 81
Treatment, Dietary, of skin tuberculosis, 209
—— of lupus, Sanatorium, 515
Tubercle bacilli, Comparison of tissue reactions to pulmonary infection with, in animals of varying resistance, 270
—— ——, cultivation of, from sputum, Comparison of certain media for, 259
Tuberculin and Schilling blood differential count in diagnosis and classification of tuberculosis, 377
——, Effect of, on spermatozoa from normal and tuberculous guinea pigs, 401
——, hypersensitiveness to, in guinea pigs, Production of tuberculous tissue and, 595
—— ointment, Tape test with, 308
—— reacting cattle, skin lesions of, Study of so-called, 600
—— tests, Pirquet and intracutaneous, Comparative sensitiveness of, 465
Tuberculoma of brain, 171
Tuberculoprotein, allergy and anaphylaxis to, Sensitization of guinea pigs and production of, 291

Tuberculosis, Alcohol and, 217
—— and leukaemia, 32
—— —— tuberculous infection among nurses, 474
——, Blood-pressure in, 342
—— case-finding, Fluoroscopy in, 71
——, Correlation in 150 clinical cases of, and underlying pathological changes as shown by serial X-ray films, 488
——, diagnosis and classification, Tuberculin and Schilling blood differential count in, 377
—— dispensary practice in New Haven, Connecticut, 611
——, emotion in, Rôle of, 315
——, Generalized, complicated by presence of yeast-like organisms, 348
——, knowledge of, Recent developments in our, 121
——, laryngeal, Costa and red-cell sedimentation reactions in, 92
—— of lungs, experimental, Localized, 143
—— patients, Effects of change of climate and altitude on, 247
——, Preventive and therapeutic measures in, since Koch, 529
——, Protection against, with *BCG* in guinea pigs, 6
——, pulmonary, activity in, current conception of, Protest against, 101
——, ——, Benign, with diabetes, 47
——, ——, filtered-air chambers in, Use of, 508
——, ——, Gastric function in, 330
——, ——, immobilization in, Appliance for, 375
——, ——, in American Negro and white race, Pathological anatomy of, 411
——, skin, treatment of, Dietary, 209
—— trained nurse, The, 81
Tuberculous cavities, adherent, Closure of, by combined artificial pneumothorax and phrenicectomy, 355
——, embolic, and pyogenic pulmonary abscesses, Comparison of pathological changes in, 150
—— guinea pigs, Effect of tuberculin on spermatozoa from normal and, 401
Tuberculous infection by way of female genital tract, Study of, 589
—— ——, primary, pathogenesis of, Studies on. I. The regressive lesions, 559
—— ——, ——, —— ——, —— ——. II. Tendencies in adult primary tuberculous infection, 575
—— ——, Tuberculosis and, among nurses, 474
—— tissue and hypersensitiveness to tuberculin in guinea pigs, Production of, 595

Varying resistance, animals of, Comparison of tissue reactions to pulmonary infection with tubercle bacilli in, 270
VORWALD, ARTHUR J. A comparison of tissue reactions to pulmonary infection with tubercle bacilli in animals of varying resistance, 270
——, —— ——., AND DONALDSON, LILIAN C. The effect of tuberculin on spermatozoa from normal and tuberculous guinea pigs, 401

WALSH, JOSEPH. The tuberculosis trained nurse, 81
WESSLER, H., AND HENNELL, HERMAN. Benign pulmonary tuberculosis with diabetes, 47
White race, Pathological anatomy of pulmonary tuberculosis in American Negro and, 411
WOLFF, ERNST, with assistance of TEITLER, MAX H. A tape test with tuberculin ointment, 308

X-ray films, serial, Correlation of blood counts in 150 clinical cases of tuberculosis and underlying pathological changes as shown by, 488

Yeast-like organisms, Generalized tuberculosis complicated by presence of, 348

ZACKS, DAVID, POUTAS, J. J., AND ARONSON, JOSEPH D. The comparative sensitiveness of the Pirquet and the intracutaneous tuberculin tests, 465